FILED ELECTRONICALLY ON

April 9, 2008

APPELLANTS' BRIEF Address to: Mail Stop: Appeal Brief-Patents Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Application Number	10/719,007
	Confirmation Number	9101
	Attorney Docket No.	DURE-007CON2
	Filing Date	November 20, 2003
	First Named Inventor	Johnson, Randolph M.
	Examiner	Ghali, Isis A. D.
	Group Art	1615
	Title: *Devices and Methods for Pain Management*	

Sir:

This Brief is filed in support of Appellants' appeal from the Examiner's Rejection dated March 14, 2007. No claims have been allowed, and Claims 48-99 are pending. Claims 48-99 are appealed. A Notice of Appeal was filed on September 12, 2007. Appellants petition for a five-month extension of time, making this Brief due by April 12, 2008. Accordingly, this Appeal Brief is timely filed.

The Board of Appeals and Interferences has jurisdiction over this appeal pursuant to 35 U.S.C. §134.

Provided herewith is an authorization to charge the amount of $510.00 to cover the fee required under 37 C.F.R. §41.20(b)(2) for filing Appellants' Brief. In the unlikely event that the fee transmittal or other papers are separated from this document and/or other fees or relief are required, Appellants petition for such relief, including extensions of time, and authorize the Commissioner to charge any fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 which may be required by this paper, or to credit any overpayment, to deposit account number 50-0815, reference no. DURE-007CON2.

TABLE OF CONTENTS

REAL PARTY IN INTEREST

The inventors named on this patent application assigned their entire rights in the invention to Durect Corporation.

RELATED APPEALS AND INTERFERENCES

There are currently no other appeals or interferences known to Appellants, the undersigned Appellants' representative, or the assignee to whom the inventors assigned their rights in the instant case, which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal.

STATUS OF CLAIMS

The present application was filed on November 20, 2003, with Claims 1-47. During the course of prosecution, Claims 1-47 were canceled and new claims 48-99 were added. Claims 48-99 are pending and under examination in the present application. Claims 48-99 stand rejected and are appealed herein.

STATUS OF AMENDMENTS

No amendments to the Claims were filed subsequent to issuance of the Final Rejection.

SUMMARY OF CLAIMED SUBJECT MATTER

The claimed invention is drawn to methods for providing analgesia in a subject by delivering a composition comprising fentanyl or a fentanyl congener to the subject. A feature of the invention is that the composition is administered to the subject using an implantable convective delivery system. An additional feature of the invention is that the composition is delivered from the system at a low volume rate.

Below is a description of each appealed independent claim, each dependent claim argued separately, and where support for each can be found in the specification.

Independent Claim 48 is directed to a method for providing analgesia in a subject, said method comprising delivering a composition comprising fentanyl or a fentanyl congener (see page 16, lines 2-7) to the subject, wherein the composition is administered to the subject using an implantable convective delivery system (see page 6, lines 20-24), is delivered from the system for 48 hours or more (see page 23, lines 13-16) at a low volume rate of 2 ml/day or less (see page 24, lines 5-11) and is sufficient to provide analgesia in the subject (see page13, lines 1-5).

Dependent Claim 53 is directed to the method of Claim 49, which is directed to the method of Claim 48. As such, Claim 53 is directed to the method of Claim 48, wherein the composition is delivered using a patterned delivery regime (see page 24, lines 5-11), and wherein the composition is delivered over an extended period of time (see page 23, lines 12-27).

Dependent Claim 54 is directed to the method of Claim 53, wherein the composition is delivered for a period of about 72 hours (see page 23, lines 12-27).

Dependent Claim 55 is directed to the method of Claim 53, wherein the composition is delivered for a period from 2 to 5 days (see page 26, lines 5-20).

Dependent Claim 56 is directed to the method of Claim 53, wherein the composition is delivered for a period of at least about 100 days (see page 26, lines 5-20).

Dependent Claim 59 is directed to the method of Claim 48, wherein the composition is delivered to the subject at a volume rate of from about 0.01 μl/day to about 100 μl/day (see page 29, lines 15-23).

Dependent Claim 60 is directed to the method of Claim 48, wherein the composition is delivered to the subject at a volume rate of from about 0.04 μl/day to about 10 μl/day (see page 29, lines 15-23).

Dependent Claim 61 is directed to the method of Claim 48, wherein the composition is delivered to the subject at a volume rate of from about 0.2 μl/day to about 5 μl/day (see page 29, lines 15-23).

Dependent Claim 62 is directed to the method of Claim 48, wherein the composition is delivered to the subject at a volume rate of from about 0.5 μl/day to about 1 μl/day (see page 29, lines 15-23).

Independent Claim 63 is directed to a method for providing analgesia in a subject, said method comprising delivering to the subject a composition comprising fentanyl or a fentanyl congener (see page 16, lines 2-7), wherein said fentanyl or fentanyl congener is present in the composition at a concentration of about 0.5 mg/ml to about 500 mg/ml or greater (see page 18, line 24 – page 19, line 1), and further wherein the composition is administered to the subject using an implantable convective delivery system (see page 6, lines 20-24), is delivered from the system at a low volume rate of about 2 ml/day or less (see page 24, lines 5-11) and is sufficient to provide analgesia in the subject (see page13, lines 1-5).

Dependent Claim 67 is directed to the method of Claim 63, wherein the fentanyl or fentanyl congener is present in the composition at a concentration of at least about 2 to at least about 10,000 times greater than the solubility of fentanyl or fentanyl congener in aqueous solution (see page 18, lines 15-23).

Dependent Claim 69 is directed to the method of Claim 63, wherein the fentanyl or fentanyl congener is present in the composition at a concentration of from about 1 mg/ml to about 400 mg/ml (see page 18, line 24 – page 19, line 27).

Dependent Claim 70 is directed to the method of Claim 63, wherein the fentanyl or fentanyl congener is present in the composition at a concentration of from about 50 mg/ml to about 400 mg/ml (see page 18, line 24 – page 19, line 27).

Dependent Claim 71 is directed to the method of Claim 63, wherein the fentanyl or fentanyl congener is present in the composition at a concentration of from about 75 mg/ml to about 300 mg/ml (see page 18, line 24 – page 19, line 27).

Dependent Claim 72 is directed to the method of Claim 63, wherein the fentanyl or fentanyl congener is present in the composition at a concentration of from about 100 mg/ml to about 250 mg/ml (see page 18, line 24 – page 19, line 27).

Dependent Claim 78 is directed to the method of Claim 74, which is directed to the method of Claim 63. As such, Claim 78 is directed to the method of Claim 63, wherein the composition is delivered using a patterned delivery regime (see page 24, lines 5-11), and wherein the composition is delivered over an extended period of time (see page 23, lines 12-27).

Dependent Claim 80 is directed to the method of Claim 78, wherein the composition is delivered for a period from about 2 to 5 days (see page 23, lines 12-27).

Dependent Claim 81 is directed to the method of Claim 78, wherein the composition is delivered for a period of at least about 100 days (see page 23, lines 12-27).

Independent Claim 84 is directed to a method for providing analgesia in a subject, said method comprising delivering to the subject a composition comprising fentanyl or a fentanyl congener (see page 16, lines 2-7), wherein the composition is administered to the subject using an implantable convective delivery system (see page 6, lines 20-24), the composition is delivered from the system for 48 hours or more (see page 23, lines 13-16) at a low volume rate sufficient to deliver from about 0.01 μg/hour to about 200 μg/hour (page 29, lines 24-27) of the fentanyl or fentanyl congener to the subject, and further wherein said amount of delivered fentanyl or fentanyl congener is sufficient to establish a systemic analgesic effect in the subject (see page13, lines 1-5).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 48-99 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Magruder et al. (US 5,057,318) (referred to hereinafter as "Magruder") in view of Nelson et al. (US 5,980,927) (referred to hereinafter as "Nelson").

ARGUMENT

Claims 48-99 are not obvious under 35 U.S.C. § 103(a) over Magruder in view of Nelson

The Appellants will argue the Claims in the following groups: Group 1 (Claims 48-52, 57, 58 and 92), Group 2 (Claim 53), Group 3 (Claim 54), Group 4 (Claim 55), Group 5 (Claim 56), Group 6 (Claim 59), Group 7 (Claim 60), Group 8 (Claim 61), Group 9 (Claim 62), Group 10 (Claims 63-66, 68, 73-77, 79, 82, 83, 93 and 95-99), Group 11 (Claim 67), Group 12 (Claim 69) Group 13 (Claim 70), Group 14 (Claim 71), Group 15 (Claim 72), Group 16 (Claim 78), Group 17 (Claim 80), Group 18 (Claim 81), Group 19 (Claims 84-91 and 94).

The Patent Office bears the burden of establishing a *prima facie* case of obviousness under 35 U.S.C. § 103(a).[1] In order to meet its burden, the Office must first demonstrate that the prior art teaches or suggests all the claimed limitations. *See Pharmastem Therapeutics, Inc. v. Viacell, Inc.*, wherein the Federal Circuit states "the burden falls on the patent challenger to show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to attempt to make the composition or device, or carry out the claimed process, and would have had a reasonable expectation of success in doing so."[2]

Furthermore, the Supreme Court has stated that "it will [often] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether

1 *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988).
2 *Pharmastem Therapeutics, Inc. v. Viacell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007).

there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue."[3]

In reviewing its own prior precedent, the Supreme Court in *KSR* emphasized that consideration of prior art that teaches away from the claimed invention is also relevant to the determination of obviousness. The Court stated that ***"when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious."***[4] See also, *Dystar Textilfarben GmbH v. C.H. Patrick Co.*, wherein the Federal Circuit stated that "[once] all claim limitations are found in a number of prior art references, the factfinder must determine '[w]hat the prior art teaches, ***whether it teaches away from the claimed invention***, and whether it motivates a combination of teachings from different references.'"[5]

Finally, as recognized by the Office in the MPEP, "[i]f [the] proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification."[6] The Federal Circuit stated a similar principle in *In re Gordon*, indicating that where the proposed modification would render the prior art invention unsatisfactory for its intended purpose, the prior art invention effectively teaches away from the proposed modification.[7]

As set forth in the arguments below, the Appellants contend that the proposed combination of references fails to teach or suggest each and every element of the claimed invention. In addition, Appellants contend that the cited references teach away from the proposed combination. Finally, Appellants contend that there would have been no apparent reason to combine the cited references in the manner suggested by the Examiner.

---

3 *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007). See also, 72 FR 57526, 57529.
4 *Id.* at 1740 (citing *United States v. Adams*, 383 U.S. 39, 40) (emphasis added).
5 *Dystar Textilfarben GmbH v. C.H. Patrick Co.*, 464 80 U.S.P.Q.2d 1641, 1646 (Fed. Cir. 2006), *citing In re Fulton*, 391 F.3d 1195, 1199-1200 (Fed. Cir. 2004) (emphasis added).
6 M.P.E.P § 2143.01.
7 *In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984).

Group 1: Claims 48-52, 57, 58 and 92

Independent Claim 48 is directed to a method for providing analgesia in a subject, said method comprising delivering a composition comprising fentanyl or a fentanyl congener to the subject, wherein the composition is administered to the subject using an implantable convective delivery system, is delivered from the system for 48 hours or more at a low volume rate of 2 ml/day or less and is sufficient to provide analgesia in the subject.

Nelson teaches away from the proposed combination with Magruder

Nelson solves the problem of providing analgesia in a subject in a completely different manner than that employed by Magruder. Rather than administering a drug systemically as disclosed in Magruder, Nelson provides a device and method for administering an analgesic directly to the neuraxis of an organism.

Nelson states that "[t]he current regimen for treatment of these patients is systemic administration of relatively high doses of analgesics by for example oral, subcutaneous, intramuscular, intravenous and related routes on a daily or continuous basis."[8] Nelson goes on to describe problems associated with various methods of systemic administration of opioid analgesics. See, for example, Nelson at column 1, lines 28-49. Finally, Nelson indicates that "[t]he present invention provides **an alternative means** for achieving continuous central nervous system administration of an analgesic **into the neuraxis via intraventricular, epidural, intrathecal and related routes** for those suffering chronic pain **and is directed to solving one or more of the problems noted above.**"[9]

By describing the various problems associated with systemic administration of opioid analgesics, and by offering its own device and method as an alternative, Nelson clearly ***teaches away*** from the systemic administration of opioid analgesics such as fentanyl or fentanyl congeners.

8 Nelson at column 1, lines 23-27.
9 *Id.* at column 2, lines 25-31.

In direct contrast to Nelson, Magruder directs **systemic administration** of drug. Specifically, Magruder discloses implantation of a device into the muscle tissue of an animal, the subcutaneous space, the vaginal cavity, or the peritoneal cavity.[10] See also, Magruder at column 10, lines 41-45, indicating that the "devices can be used for dispensing a beneficial agent in the anal-rectal passageway, in the cervical canal, as an artificial gland, in the vagina, as a subcutaneous implant and the like." In the context of the delivery of opioid analgesics such as fentanyl or fentanyl congeners, **delivery at these sites constitutes systemic administration**. This is because, as indicated in Nelson, these drugs act on receptors found in the neuraxis and must reach their central site of action through diffusion across the blood-brain barrier.[11]

In short: Magruder points the ordinarily skilled artisan toward use of a device to achieve systemic delivery. Nelson states a goal of avoiding systemic delivery, and provides a method to accomplish delivery directly to the central nervous system. As such, one of ordinary skill in the art would be directed away from the proposed combination with Magruder given Nelson's teaching that the systemic administration of these analgesics is undesirable.

Furthermore, the instant claims, by virtue of the recited delivery rates and administration periods, require use of a highly concentrated formulation of fentanyl or fentanyl congener. A high concentration formulation of this type would be unnecessary in the context of a device such as Nelson's which operates by diffusion and is designed for local delivery to the neuraxis. Furthermore, because Nelson teaches implantation and delivery directly to the drug's site of action, a person of ordinary skill in the art would be directed away from the use of a highly concentrated formulation of a highly potent drug such as fentanyl or a fentanyl congener. Delivery of such a formulation directly to the site of drug action, e.g., via implantation in a brain ventricle, would be associated with an extremely high risk of negative side effects. As such, Appellants submit that Nelson

10 Magruder at column 3, lines 50-56.
11 Nelson at column 1, lines 17-48.

teaches away from the claimed invention which, by virtue of the recited delivery rates and administration periods requires use of a high-concentration formulation.

Modification of the Magruder reference with the teaching of the Nelson reference renders the device inoperable for its intended purpose

By selectively focusing on Nelson's alleged discussion of fentanyl and sufentanil as exemplary opioids, the Examiner ignores the remaining disclosure of the Magruder and Nelson references relating to the nature of the devices in these references. The device of Nelson consists of a biocompatible polymer matrix body loaded with an analgesic. Magruder's device contains a liquid drug formulation. [12] There is absolutely no indication in either Nelson or Magruder that the device of Magruder is compatible for use with a drug in a matrix, nor does Nelson indicate the polymer matrix can carry a liquid formulation. Indeed, given the mechanism of Magruder's device, substituting the liquid formulation with the drug-containing matrix of Nelson would render the Magruder device completely inoperable and thus unsatisfactory for its intended purpose. A solid polymer matrix body as described in Nelson would essentially clog the device of Magruder, thereby preventing the expandable driving means from pushing the beneficial agent composition from the delivery system. This fact would be readily apparent to a person of ordinary skill in the art provided with the disclosures of both Nelson and Magruder.

As indicated by the Federal Circuit in *In re Gordon*, where the proposed modification would render the prior art invention unsatisfactory for its intended purpose, the prior art invention effectively teaches away from the proposed modification. [13]

As such, Appellants submit that the references cannot be properly combined to arrive at the claimed invention.

12 Magruder at column 16, lines 4-19.
13 *In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984).

The proposed modification or combination would change the principle of operation of the invention being modified

The devices of Magruder and Nelson have completely different principles of operation. The Magruder system is a ***convective*** system, while the Nelson apparatus is a polymeric matrix that relies upon ***diffusion*** for drug delivery to the neuraxis. Convection involves an active process of conveying (such as via a pump), whereas diffusion does not. As such, modification of Magruder with the analgesic loaded polymer matrix body described by Nelson would alter the principle of operation of the Magruder system.

Where the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious.[14] In view of the different principles of operation of the Magruder and Nelson systems, there would have been no apparent reason for a person of ordinary skill in the art to combine the references in an attempt to arrive at the claimed invention.

The proposed combination of references fails to teach or suggest each and every element of the claimed invention

The Examiner's rejection is flawed in that the combination of Magruder and Nelson fails to teach or suggest each and every element of independent Claim 48.

In maintaining this rejection, the Examiner states that Magruder teaches implantable osmotic drug delivery devices that can be highly loaded with beneficial agents and are able to deliver active beneficial agents at a controlled rate continuously over time and over a broad range of dosage delivery rates according to predetermined time release patterns.[15] The Examiner also states that Magruder teaches that analgesics are suitable for delivery by the implantable osmotic delivery device.[16] The Examiner acknowledges that Magruder

14 *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959).
15 Final Office Action mailed 3-14-08, page 3.
16 *Id.*

does not teach that the device may be used to deliver fentanyl or a fentanyl congener.[17] The Examiner also acknowledges that Magruder does not teach the doses and periods of delivery claimed in the instant application.[18]

In an attempt to remedy the deficiencies in Magruder, the Examiner cites Nelson for an alleged teaching of the administration of fentanyl and sufentanil. The Examiner asserts that it would have been obvious to one of ordinary skill in the art at the time of the invention to replace the analgesic mentioned in Magruder with fentanyl or sufentanil as disclosed by Nelson.[19]

Claim 48 requires that the composition comprising fentanyl or a fentanyl congener is delivered from the system for 48 hours or more at a low volume rate of 2 ml/day or less and is sufficient to provide analgesia in the subject. There is absolutely no indication in Magruder that the disclosed devices are capable of delivering any composition for 48 hours or more at a low volume rate of 2ml/day or less, much less the compositions of the instant application. In fact, Appellants find no discussion whatsoever in Magruder of any specific volume based delivery rates. Instead, Magruder merely makes the unsupported statement that an object of the invention is to provide a delivery system manufactured as an osmotic device that possesses the ability to deliver the beneficial drug "over a broad range of dosage delivery rates according to the predetermined time-release pattern to the biological recipient over time."[20] Appellants note that Magruder fails to provide even a single example of a volume based delivery rate achieved using its delivery system. The complete lack of disclosure with respect to this required claim element cannot be taken as a suggestion to delivery a composition, much less a fentanyl or fentanyl congener composition, in the manner claimed in the instant application.

---

17 *Id.*
18 *Id.*
19 *Id.* at page 4.
20 Magruder, column 3, lines 35-42.

The Examiner relies on Nelson solely for an alleged teaching of the administration of fentanyl and sufentanil. However, since Nelson fails to disclose the claimed delivery rates, the addition of Nelson fails to cure the acknowledged deficiencies in Magruder.

The Examiner asserts, however, that "the amount and delivery rate of the active agent do not impart patentability to the claims, absent evidence to the contrary."[21] The Examiner also asserts that "[i]t is within the skilled artisan to manipulate the amount of the active agent to achieve a specific delivery profile according to specific patient need."[22]

As discussed extensively during the prosecution of the instant application, Claim 48 provides a method where an exceptionally small volume rate (2 ml/day or less) of a composition containing fentanyl or a fentanyl congener active agent is delivered for 48 hours or more, yet the method is nonetheless able to achieve therapeutically effective analgesia in the subject. Accomplishing the elements of Claim 48 would require a high concentration fentanyl/fentanyl congener formulation. Without reference to the Appellants disclosure, the use of such a low volume rate to achieve analgesia is counter-intuitive, in that one would logically expect that the efficacy of fentanyl/fentanyl congener administration would be negligible at such a low volume delivery rate. Moreover, the Examiner has failed to provide any evidence that a high concentration fentanyl/fentanyl congener formulation sufficient to enable the claimed delivery rates was in the art prior to the March 18, 1999 priority date of the instant application.

Instead the art points to the use of high volume rates of delivery in order to provide analgesia. See, for example, page 4 of the instant application, wherein the Appellants discuss the work of Paix et al. (1995) *Pain* 63:263-9, cited in the IDS filed in the instant application on August 13, 2004.

> Paix et al. (1995 Pain 63:263-9), for example, discloses the use of subcutaneous fentanyl and sufentanil as an alternative therapy in a small number of patients who suffered significant side effects associated with

21 Final Office Action mailed 3-14-08, page 4.

> administration of morphine. In Paix et al., the drug was infused into the subcutaneous space **at relatively large volume rates (e.g., on the order of 3 mL/day to 40 mL/day)** via an external syringe driver. **The treatment method disclosed by Paix et al. has several major disadvantages that render it impractical for long-term therapy**. First, the provision of drug from an external source adversely affects mobility of the patient and is therefore inconvenient for ambulatory patients, increases the risk of infections at the subcutaneous delivery site and provides an opportunity for drug to be diverted for illicit uses. Second, **the infusion of large volumes of fluid may result in tissue damage or edema at the site of infusion. In addition, the absorptive capacity of the subcutaneous space limits the volume of fluid that can be delivered (see, e.g., Anderson et al., supra), and this volumetric limitation can in turn limit the amount of drug that can be administered**.[23]

As evidenced by the instant specification and the references cited therein, prior attempts to deliver fentanyl and sufentanil required the use of relatively large volume rates (e.g., on the order of 3 ml/day to 40 ml/day). For example, see Paix et al. at page 267, wherein the authors indicate that the delivery of 2200μg of fentanyl in 24 hours required the delivery of a volume of at least 44ml.

Furthermore, the Physician's Desk Reference ("PDR"), Thomson Healthcare, Montvale, NJ, (2001), pages 826 and 831-832 of which were cited in the IDS filed in the instant application on June 20, 2006, suggests that the fentanyl and sufentanil formulations available prior to the priority date of the instant application were of significantly lower concentration than those disclosed in the instant application. By way of example, Page 826 of the PDR describes a fentanyl citrate injection formulation marketed by Baxter Pharmaceutical. The described "Fentanyl Citrate Injection is a sterile, non-pyrogenic solution for intravenous or intramuscular use as a potent narcotic analgesic. **Each mL contains fentanyl citrate equivalent to 50mcg (0.05mg) fentanyl base in Water for**

---

22 *Id.*

Injection."[24] Similarly, pages 831-832 of the PDR describe a sufentanil citrate injection formulation. The described "Sufentanil Citrate Injection, USP is a sterile, nonpyrogenic, aqueous solution for intravenous and epidural injection. **Each mL contains sufentanil citrate equivalent to 50mcg (0.05 mg) of sufentanil in Water for Injection.**"[25]

Thus, even after the priority date of the instant application, the commercially available formulations of fentanyl and sufentanil contained relatively low concentrations of the active agents.

Appellants' specification provides supporting examples of high concentration formulations. For example, at pages 35-36 of the instant specification, Appellants describe the preparation of sufentanil formulations having sufentanil concentrations of 77mg/ml, 248 mg/ml, 310 mg/ml and 397 mg/ml.

Appellants' ability to produce such formulations provided exceptional benefit to the art in that now, methods of pain management can be carried out by administering exceptionally small volumes of the fentanyl or fentanyl congener formulation to a site. This avoids accumulation of excessive drug at the delivery site (pooling or depot effect) since the rate of administration is at or only slightly higher than the rate of removal of the drug from the delivery site.[26]

Thus, the claimed invention is not simply about manipulating delivery volumes and concentrations of drug. Rather, the claims, by virtue of the recited delivery rates and administration periods, require use of a concentrated formulation of fentanyl or fentanyl congener, which formulation has a drug concentration higher than that earlier available in the art.

Given the relatively low concentration formulations available prior to Appellants' May 18, 1999 priority date, a person of ordinary skill in the art would have had no reasonable

---

23 Specification, page 4, lines 7-24 (emphasis added).
24 Physician's Desk Reference, Thomson Healthcare, Montvale, NJ, (2001), page 826 (emphasis added).
25 *Id.* at pages 831-832 (emphasis added).
26 Specification at page 24, line 24 – page 25, line 6 (emphasis added).

expectation of success with respect to providing analgesia in a subject via delivery of fentanyl or a fentanyl congener at the low volume rates described in the instant claims.

For the reasons set forth above, Appellants submit that the combination of Magruder and Nelson fails to render Claim 48 *prima facie* obvious. Since Claims 49-52, 57, 58 and 92 each depend ultimately from Claim 48, the arguments presented above apply with equal force to the rejection of each of these claims.

As such, the Appellants respectfully request reversal of the rejection of Claims 48-52, 57, 58 and 92 under 35 U.S.C. §103(a).

Group 2: Claim 53

Due to its ultimate dependency on Claim 48, Claim 53 is not obvious over Magruder in view of Nelson for at least the reasons detailed above for the claims of Group 1.

In addition to the limitations of Claim 48, Claim 53 also requires that the composition is delivered using a ***patterned delivery regime*** and that the composition is ***delivered over an extended period of time.***

The Examiner explicitly acknowledges that Magruder fails to teach "fentanyl and sufentanil as the analgesic drug or doses and periods of delivery, *i.e. the patterned delivery regimen, as instantly claimed.*"[27] The Examiner asserts, however, that one of ordinary skill in the art would have been motivated to use the implantable osmotic device of Magruder to deliver analgesics that need continuous delivery and manipulate the amount of analgesic and its period of delivery.

As discussed in the context of Claim 48, delivery of fentanyl or a fentanyl congener over an extended period of time using a low volume rate and a patterned delivery regime would require a high concentration fentanyl/fentanyl congener formulation. However, the Examiner has failed to provide any evidence that such a high concentration

27 Final Office Action mailed 3/14/07, page 3 (emphasis added).

fentanyl/fentanyl congener formulation was in the art prior to the March 18, 1999 priority date of the instant application.

Furthermore, Appellants have cited references indicating that prior to the priority date of the instant application, relatively large volumes were required to maintain a volume rate sufficient to deliver the a fentanyl or fentanyl congener formulation over an extended period of time and provide analgesia in a subject. See, e.g., the discussion of Paix et al. set forth in the discussion of Group I above. It should be readily apparent to the person of ordinary skill in the art that a device designed to hold such a large volume would not be suitable for implantation into a subject for an extended period of time.

As the Examiner relies on Nelson solely for an alleged teaching of fentanyl and sufentanil as analgesics, the combination of Nelson with Magruder fails to remedy the deficiencies in Magruder with respect to the elements of Claim 53.

In view of the above, Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness with respect to the claimed invention. Reversal of the rejection of Claim 53 under 35 U.S.C. §103(a) is thus respectfully requested.

Group 3: Claim 54

Due to its ultimate dependency on Claim 48, Claim 54 is not obvious over Magruder in view of Nelson for at least the reasons detailed above for the claims of Group 1.

In addition to the limitations of Claim 48, Claim 54 also requires that the composition is delivered for a period of about ***72 hours***.

Without repeating the arguments presented above with respect to Group 2, Appellants submit that these arguments apply with at least equal force, if not even greater force, to the rejection of Claim 54 which depends on Claim 53 and which recites a specific extended period of delivery of about 72 hours.

Moreover, delivery of a fentanyl/fentanyl congener composition at a low volume rate of less than 2 ml/day to provide for analgesia in a subject for about 72 hours requires a

highly concentrated fentanyl/fentanyl congener formulation. Magruder and Nelson, both individually and in combination, fail to teach or suggest this claim element.

In view of the above Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness with respect to Claim 54. Reversal of the rejection of Claim 54 under 35 U.S.C. §103(a) is thus respectfully requested.

Group 4: Claim 55

Due to its ultimate dependency on Claim 48, Claim 55 is not obvious over Magruder in view of Nelson for at least the reasons detailed above for the claims of Group I.

In addition to the limitations of Claim 48, Claim 55 also requires that the composition is delivered for a period ***from 2 to 5 days***.

Without repeating the arguments presented above with respect to Group 2, Appellants submit that these arguments apply with at least equal force, if not greater force, to the rejection of Claim 55 which depends on Claim 53 and which recites a specific extended period of delivery of 2 to 5 days.

Moreover, delivery of a fentanyl/fentanyl congener composition at a low volume rate of less than 2 ml/day to provide for analgesia in a subject for a period from 2 to 5 days requires a highly concentrated fentanyl/fentanyl congener formulation. Magruder and Nelson, both individually and in combination, fail to teach or suggest this claim element.

In addition, the Examiner has failed to provide any evidence that such a high concentration fentanyl/fentanyl congener formulation was in the art prior to the March 18, 1999 priority date of the instant application.

In view of the above Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness with respect to Claim 55. Reversal of the rejection of Claim 55 under 35 U.S.C. §103(a) is thus respectfully requested.

Group 5: Claim 56

Due to its ultimate dependency on Claim 48, Claim 56 is not obvious over Magruder in view of Nelson for at least the reasons detailed above for the claims of Group I.

In addition to the limitations of Claim 48, Claim 56 also requires that the composition is delivered for a period of ***at least about 100 days***.

Without repeating the arguments presented above with respect to Group 2, Appellants submit that these arguments apply with at least equal force, if not greater force, to the rejection of Claim 56 which depends on Claim 53 and which recites a specific extended period of delivery of ***at least about 100 days***. This period of time is significantly longer than that recited in each of Claims 54 and 55.

Moreover, delivery of a fentanyl/fentanyl congener composition at the low volume rate of less than 2 ml/day for a period of at least about 100 days, wherein the delivery is sufficient to provide analgesia in the subject requires a highly concentrated fentanyl/fentanyl congener formulation. Magruder and Nelson, both individually and in combination, fail to teach or suggest this claim element.

In addition, the Examiner has failed to provide any evidence that such a high concentration fentanyl/fentanyl congener formulation was in the art prior to the March 18, 1999 priority date of the instant application.

In view of the above Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness with respect to Claim 56. Reversal of the rejection of Claim 56 under 35 U.S.C. §103(a) is thus respectfully requested.

Group 6: Claim 59

Due to its ultimate dependency on Claim 48, Claim 59 is not obvious over Magruder in view of Nelson for at least the reasons detailed above for the claims of Group I.

In addition to the limitations of Claim 48, Claim 59 also requires that the composition is delivered to the subject at a volume rate of from about ***0.01 µl/day to about 100 µl/day***.

Magruder fails to disclose a delivery system capable of delivering this extremely low volume rate. This complete lack of disclosure cannot be taken as a suggestion to perform the method of Claim 59.

As the Examiner relies on Nelson solely for an alleged teaching of fentanyl and sufentanil as analgesics, the combination of Nelson with Magruder fails to remedy the deficiencies in Magruder with respect to the elements of Claim 59.

Furthermore, delivery of fentanyl or a fentanyl congener at a volume rate of from about 0.01 µl/day to about 100 µl/day, for a period of 48 hours or more, wherein such delivery is sufficient to provide analgesia in a subject requires a highly concentrated fentanyl/fentanyl congener formulation. Magruder and Nelson, both individually and in combination, fail to teach or suggest this claim element.

In addition, the Examiner has failed to provide any evidence that such a high concentration fentanyl/fentanyl congener formulation was in the art prior to the March 18, 1999 priority date of the instant application.

Appellants have cited references indicating that prior to the priority date of the instant application, relatively large volumes (on the order of several mls or more per day) were required to maintain a volume rate sufficient to deliver a fentanyl or fentanyl congener formulation over an extended period of time and provide analgesia in a subject. See, e.g., the discussion of Paix et al. set forth in the discussion of Group I above. Thus, without reference to Appellants' disclosure, one of ordinary skill in the art would have had no reasonable expectation of success with respect to providing analgesia in a subject via the delivery of a fentanyl or fentanyl congener formulation at such a low volume rate.

In view of the above, Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness with respect to the claimed invention. Reversal of the rejection of Claim 59 under 35 U.S.C. §103(a) is thus respectfully requested.

Group 7: Claim 60

Due to its ultimate dependency on Claim 48, Claim 60 is not obvious over Magruder in view of Nelson for at least the reasons detailed above for the claims of Group I.

In addition to the limitations of Claim 48, Claim 60 also requires that the composition is delivered to the subject at a volume rate of from about ***0.04 µl/day to about 10 µl/day***.

Without repeating the arguments set forth with respect to Group 6, Appellants submit that these arguments apply *a fortiori* to the rejection of Claim 60 because the high end of the volume range in Claim 60 is significantly lower than that recited in Claim 59. An extremely low volume delivery rate, such as that required in Claim 60, that is sufficient to provide analgesia in a subject, requires the use of an extremely high concentration fentanyl/fentanyl congener formulation. Magruder and Nelson, both individually and in combination, fail to teach or suggest this claim element.

Furthermore, the Examiner has failed to provide any evidence that such a high concentration fentanyl/fentanyl congener formulation was in the art prior to the March 18, 1999 priority date of the instant application.

In view of the above, Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness with respect to the claimed invention. Reversal of the rejection of Claim 60 under 35 U.S.C. §103(a) is thus respectfully requested.

Group 8: Claim 61

Due to its ultimate dependency on Claim 48, Claim 61 is not obvious over Magruder in view of Nelson for at least the reasons detailed above for the claims of Group I.

In addition to the limitations of Claim 48, Claim 61 also requires that the composition is delivered to the subject at a volume rate of from about ***0.2 µl/day to about 5 µl/day***.

Without repeating the arguments set forth with respect to Group 7, Appellants submit that these arguments apply *a fortiori* to the rejection of Claim 61 because the high

end of the volume range in Claim 61 (5 μl/day) is significantly lower than that recited in Claim 60 (10 μl/day). An extremely low volume delivery rate, such as that required in Claim 61, that is sufficient to provide analgesia in a subject, requires the use of an extremely high concentration fentanyl/fentanyl congener formulation. Magruder and Nelson, both individually and in combination, fail to teach or suggest this claim element.

Furthermore, the Examiner has failed to provide any evidence that such a high concentration fentanyl/fentanyl congener formulation was in the art prior to the March 18, 1999 priority date of the instant application.

In view of the above, Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness with respect to the claimed invention. Reversal of the rejection of Claim 61 under 35 U.S.C. §103(a) is thus respectfully requested.

Group 9: Claim 62

Due to its ultimate dependency on Claim 48, Claim 62 is not obvious over Magruder in view of Nelson for at least the reasons detailed above for the claims of Group I.

In addition to the limitations of Claim 48, Claim 62 also requires that the composition is delivered to the subject at a volume rate of from about ***0.5 μl/day to about 1 μl/day***.

Without repeating the arguments set forth with respect to Group 8, Appellants submit that these arguments apply *a fortiori* to the rejection of Claim 62 because the high end of the volume range in Claim 62 (1μl/day) is significantly lower than that recited in Claim 61 (5 μl/day). An extremely low volume delivery rate, such as that required in Claim 62, that is sufficient to provide analgesia in a subject, requires the use of an extremely high concentration fentanyl/fentanyl congener formulation. Magruder and Nelson, both individually and in combination, fail to teach or suggest this claim element.

Furthermore, the Examiner has failed to provide any evidence that such a high concentration fentanyl/fentanyl congener formulation was in the art prior to the March 18, 1999 priority date of the instant application.

In view of the above, Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness with respect to the claimed invention. Reversal of the rejection of Claim 62 under 35 U.S.C. §103(a) is thus respectfully requested.

Group 10: Claims 63-66, 68, 73-77, 79, 82, 83, 93 and 95-99

Independent Claim 63 is directed to a method for providing analgesia in a subject, said method comprising delivering to the subject a composition comprising fentanyl or a fentanyl congener, wherein said fentanyl or fentanyl congener is present in the composition at a concentration of about ***0.5 mg/ml to about 500 mg/ml*** or greater, and further wherein the composition is administered to the subject using an implantable convective delivery system, is delivered from the system at a low volume rate of about 2 ml/day or less and is sufficient to provide analgesia in the subject.

Without repeating the arguments in their entirety, Appellants submit that the arguments presented in the context of Group 1 with respect to teaching away and the lack of an apparent reason to combine the references apply with equal force to the rejection of independent Claim 63.

Nelson provides a device and method for administering an analgesic directly to the neuraxis of an organism and indicates that this device is designed to avoid many of the problems associated with systemic delivery of opioid analgesics. Thus, Nelson clearly ***teaches away*** from the systemic administration of opioid analgesics such as fentanyl or fentanyl congeners as described in Magruder.

In direct contrast to Nelson, Magruder directs **systemic administration** of drug. In view of these respective teachings, one of ordinary skill in the art would have been directed away from the proposed combination of Nelson with Magruder given Nelson's teaching that the systemic administration of opioid analgesics is undesirable.

As discussed above, the claims, by virtue of the recited delivery rates and administration periods, require use of a highly concentrated formulation of fentanyl or fentanyl congener. Because Nelson teaches implantation and delivery directly to the drug's

site of action, a person of ordinary skill in the art would be directed away from the use of a highly concentrated formulation of a highly potent drug. Delivery of such a formulation directly to the site of drug action, e.g., via implantation in a brain ventricle, would be associated with an extremely high risk of negative side effects. As such, Appellants submit that Nelson teaches away from the claimed invention which, by virtue of the recited delivery rates and administration periods requires use of a high-concentration formulation.

In maintaining this rejection, the Examiner states that Magruder teaches implantable osmotic drug delivery devices that can be highly loaded with beneficial agents and are able to deliver active beneficial agents at a controlled rate continuously over time and over a broad range of dosage delivery rates according to predetermined time release patterns.[28] The Examiner also states that Magruder teaches that analgesics are suitable for delivery by the implantable osmotic delivery device.[29] The Examiner acknowledges that Magruder does not teach that the device may be used to deliver fentanyl or a fentanyl congener.[30] The Examiner also acknowledges that Magruder does not teach the doses and periods of delivery claimed in the instant application.[31]

In an attempt to remedy the deficiencies in Magruder, the Examiner cites Nelson for an alleged teaching of the administration of fentanyl and sufentanil. The Examiner asserts that it would have been obvious to one of ordinary skill in the art at the time of the invention to replace the analgesic mentioned in Magruder with fentanyl or sufentanil as disclosed by Nelson.[32]

As indicated above, Claim 63 requires that said fentanyl or fentanyl congener is present in the composition at a concentration of about 0.5 mg/ml to about 500 mg/ml or greater, said composition is delivered from the system at a low volume rate of 2 ml/day or less and is sufficient to provide analgesia in the subject. There is absolutely no discussion in Magruder of any drug concentration range, much less the claimed concentration range

28 Final Office Action mailed 3-14-08, page 3.
29 *Id.*
30 *Id.*
31 *Id.*

of fentanyl or fentanyl congener. Instead, Magruder merely makes the unsupported statement that an object of the invention is to provide a delivery system manufactured as an osmotic device that possesses the ability to deliver the beneficial drug "over a broad range of dosage delivery rates according to the predetermined time-release pattern to the biological recipient over time."[33] The complete lack of disclosure with respect to this required claim element cannot be taken as a suggestion to deliver the claimed fentanyl or fentanyl congener composition in the manner claimed in the instant application.

As the Examiner relies on Nelson solely for an alleged teaching of fentanyl and sufentanil as analgesics, the combination of Nelson with Magruder fails to remedy the deficiencies in Magruder with respect to the elements of Claim 63.

The Examiner asserts, however, that "the amount and delivery rate of the active agent do not impart patentability to the claims, absent evidence to the contrary."[34] The Examiner also asserts that "[i]t is within the skilled artisan to manipulate the amount of the active agent to achieve a specific delivery profile according to specific patient need."[35]

As discussed in connection with the claims of Group I, the formulations of fentanyl or fentanyl congeners available prior to the priority date of the instant application were relatively low concentration formulations. Evidence to support this conclusion has been provided in the form of specific citations to the specification of the instant application,[36] sections of the Paix et al. reference[37] and applicable sections of the PDR.[38]

In view of the above, arriving at the claimed concentrations of fentanyl or fentanyl congener would not have been, as the Examiner suggests, a simple matter of manipulating the amount of the active agent to achieve a specific delivery profile according to specific

---

32 *Id.* at page 4.
33 Magruder, column 3, lines 35-42.
34 Final Office Action mailed 3-14-08, page 4.
35 *Id.*
36 Specification, page 4, lines 7-24; page 18, line 14 – page 19, line 2; and pages 35-36.
37 Paix et al. (1995) *Pain* 63:263-9.
38 Physician's Desk Reference, Thomson Healthcare, Montvale, NJ, (2001), page 826 and 831-832.
39 Final Office Action mailed 3-14-08, page 4.

patient need.[39] As such, Appellants submit that the proposed combination of references fails to teach or suggest each and every element of independent Claim 63.

For the reasons set forth above, Appellants submit that the combination of Magruder and Nelson fails to render Claim 63 *prima facie* obvious. Since Claims 64-66, 68, 73-77, 79, 82, 83, 93 and 95-99 each depend ultimately from Claim 63, the arguments presented above apply with equal force each of these claims.

As such, the Appellants respectfully request reversal of the rejection of 63-66, 68, 73-77, 82, 83, 93 and 95-99 under 35 U.S.C. §103(a).

Group 11: Claim 67

Due to its ultimate dependency on Claim 63, Claim 67 is not obvious over Magruder in view of Nelson for at least the reasons detailed above for the claims of Group 10.

In addition to the limitations of Claim 63, Claim 67 also requires that the fentanyl or fentanyl congener is present in the composition at a concentration of ***at least about 2 to at least about 10,000 times greater*** than the solubility of fentanyl or fentanyl congener in aqueous solution.

As discussed above, the claims, by virtue of the recited delivery rates and administration periods, require use of a highly concentrated formulation of fentanyl or fentanyl congener. In fact, Claim 67 explicitly requires that the fentanyl/fentanyl congener in the composition is at a concentration of at least about 2 to at least about 10,000 times greater than the solubility of fentanyl or fentanyl congener in aqueous solution.

Because Nelson teaches implantation and delivery directly to the drug's site of action, a person of ordinary skill in the art would be directed away from the use of a highly concentrated formulation of such a highly potent drug. Delivery of such a formulation directly to the site of drug action, e.g., via implantation in a brain ventricle, would be associated with an extremely high risk of negative side effects.

As such, Appellants submit that Nelson teaches away from the claimed invention which requires that the fentanyl or fentanyl congener is present in the composition at a concentration of at least about 2 to at least about 10,000 times greater than the solubility of fentanyl or fentanyl congener in aqueous solution.

As evidenced by the sections of the PDR cited herein,[40] even after the priority date of the instant application, the commercially available formulations of fentanyl and sufentanil were relatively low concentration aqueous formulations, e.g. 50 μg/ml prepared in aqueous solution. As such, there would have been no reasonable expectation of success with respect to the delivery of a composition wherein the fentanyl or fentanyl congener is present in the composition at a concentration of at least about 2 to at least about 10,000 times greater than the solubility of fentanyl or fentanyl congener in aqueous solution.

In view of the above, Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness with respect to the claimed invention. Reversal of the rejection of Claim 67 under 35 U.S.C. §103(a) is thus respectfully requested.

Group 12: Claim 69

Due to its ultimate dependency on Claim 63, Claim 69 is not obvious over Magruder in view of Nelson for at least the reasons detailed above for the claims of Group 10.

In addition to the limitations of Claim 63, Claim 69 also requires that the fentanyl or fentanyl congener is present in the composition at a concentration of from ***about 1 mg/ml to about 400 mg/ml.***

Without repeating the arguments set forth with respect to Group 10, Appellants submit that these arguments apply *a fortiori* to the rejection of Claim 69 because the low end of the concentration range in Claim 69 is significantly higher than that recited in Claim 63. A person of ordinary skill in the art, without reference to Appellants disclosure, would

40 Physician's Desk Reference, Thomson Healthcare, Montvale, NJ, (2001), page 826 and 831-832.

have had no reasonable expectation of success with respect to the claimed concentration range.

In view of the above, Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness with respect to the claimed invention. Reversal of the rejection of Claim 69 under 35 U.S.C. §103(a) is thus respectfully requested.

Group 13: Claim 70

Due to its ultimate dependency on Claim 63, Claim 70 is not obvious over Magruder in view of Nelson for at least the reasons detailed above for the claims of Group 10.

In addition to the limitations of Claim 63, Claim 70 also requires that the fentanyl or fentanyl congener is present in the composition at a concentration of from ***about 50 mg/ml to about 400 mg/ml***.

Without repeating the arguments set forth with respect to Group 12, Appellants submit that these arguments apply *a fortiori* to the rejection of Claim 70 because the low end of the concentration range in Claim 70 is significantly higher than that recited in Claim 69.

In view of the above, Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness with respect to the claimed invention. Reversal of the rejection of Claim 70 under 35 U.S.C. §103(a) is thus respectfully requested.

Group 14: Claim 71

Due to its ultimate dependency on Claim 63, Claim 71 is not obvious over Magruder in view of Nelson for at least the reasons detailed above for the claims of Group 10.

In addition to the limitations of Claim 63, Claim 71 also requires that the fentanyl or fentanyl congener is present in the composition at a concentration of from about ***75 mg/ml to about 300 mg/ml***.

Without repeating the arguments set forth with respect to Group 13, Appellants submit that these arguments apply *a fortiori* to the rejection of Claim 71 because the low end of the concentration range in Claim 71 is significantly higher than that recited in Claim 70.

Furthermore, because Nelson teaches delivery directly to the drug's site of action, a person of ordinary skill in the art would be directed away from the use of the highly concentrated formulation of the instant claim. Delivery of such a formulation directly to the site of drug action, e.g., via implantation in a brain ventricle, would be associated with an extremely high risk of negative side effects. As such, Appellants submit that Nelson teaches away from the claimed invention which requires that the fentanyl or fentanyl congener is present in the composition at a concentration of from about 75 mg/ml to about 300 mg/ml.

In view of the above, Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness with respect to the claimed invention. Reversal of the rejection of Claim 71 under 35 U.S.C. §103(a) is thus respectfully requested.

Group 15: Claim 72

Due to its ultimate dependency on Claim 63, Claim 72 is not obvious over Magruder in view of Nelson for at least the reasons detailed above for the claims of Group 10.

In addition to the limitations of Claim 63, Claim 72 also requires that the fentanyl or fentanyl congener is present in the composition at a concentration of from about ***100 mg/ml to about 250 mg/ml***.

Without repeating the arguments set forth with respect to Group 14, Appellants submit that these arguments apply *a fortiori* to the rejection of Claim 72 because the low end of the concentration range in Claim 72 is significantly higher than that recited in Claim 71.

Furthermore, because Nelson teaches delivery directly to the drug's site of action, a person of ordinary skill in the art would be directed away from the use of the highly concentrated formulation of the instant claim. Delivery of such a formulation directly to the site of drug action, e.g., via implantation in a brain ventricle, would be associated with an extremely high risk of negative side effects. As such, Appellants submit that Nelson teaches away from the claimed invention which requires that the fentanyl or fentanyl congener is present in the composition at a concentration of from about 100 mg/ml to about 250 mg/ml.

In view of the above, Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness with respect to the claimed invention. Reversal of the rejection of Claim 72 under 35 U.S.C. §103(a) is thus respectfully requested.

Group 16: Claim 78

Due to its ultimate dependency on Claim 63, Claim 78 is not obvious over Magruder in view of Nelson for at least the reasons detailed above for the claims of Group 10.

In addition to the limitations of Claim 63, Claim 78 also requires that the composition is delivered using a patterned delivery regime and that the composition is delivered over an extended period of time.

This additional limitation was discussed above in the context of Group 2 (Claim 53). For the sake of brevity, these arguments will not be repeated. However, Appellants submit that these arguments apply with equal force to the rejection of Claim 78.

In view of the above, Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness with respect to the claimed invention. Reversal of the rejection of Claim 78 under 35 U.S.C. §103(a) is thus respectfully requested.

Group 17: Claim 80

Due to its ultimate dependency on Claim 63, Claim 80 is not obvious over Magruder in view of Nelson for at least the reasons detailed above for the claims of Group 10.

In addition to the limitations of Claim 63, Claim 80 also requires that the composition is delivered for a period from about 2 to 5 days.

Without repeating the arguments presented above with respect to Group 16, Appellants submit that these arguments apply with equal force to the rejection of Claim 80 which depends on Claim 63 and which recites a specific extended period of delivery of 2 to 5 days.

In view of the above, Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness with respect to the claimed invention. Reversal of the rejection of Claim 80 under 35 U.S.C. §103(a) is thus respectfully requested.

Group 18: Claim 81

Due to its ultimate dependency on Claim 63, Claim 81 is not obvious over Magruder in view of Nelson for at least the reasons detailed above for the claims of Group 10.

In addition to the limitations of Claim 63, Claim 81 also requires that the composition is delivered for a period of at least about 100 days.

Without repeating the arguments presented above with respect to Group 17, Appellants submit that these arguments apply with equal force to the rejection of Claim 81 which depends on Claim 63 and which recites a specific extended period of delivery of at least about 100 days.

Furthermore, as the period of delivery in Claim 56 is significantly longer than that recited in Claim 80, the arguments presented above with respect to Group 17 apply *a fortiori* to the rejection of Claim 81.

In view of the above, Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness with respect to the claimed invention. Reversal of the rejection of Claim 81 under 35 U.S.C. §103(a) is thus respectfully requested.

Group 19: Claims 84-91 and 94

Independent Claim 84 is directed to a method for providing analgesia in a subject, said method comprising delivering to the subject a composition comprising fentanyl or a fentanyl congener, wherein the composition is administered to the subject using an implantable convective delivery system, the composition is delivered from the system for 48 hours or more at a low volume rate sufficient to deliver from about 0.01 μg/hour to about 200 μg/hour of the fentanyl or fentanyl congener to the subject, and further wherein said amount of delivered fentanyl or fentanyl congener is sufficient to establish a systemic analgesic effect in the subject.

Without repeating the arguments in their entirety, Appellants submit that the arguments presented in the context of Group 1 with respect to teaching away and the lack of an apparent reason to combine the references, apply equally to the rejection of independent Claim 84.

In short: Magruder points the ordinarily skilled artisan toward use of a device to achieve systemic delivery. Nelson states a goal of avoiding systemic delivery, and provides a method to accomplish delivery directly to the central nervous system. As such, one of ordinary skill in the art would be directed away from the proposed combination with Magruder given Nelson's teaching that the systemic administration of these analgesics is undesirable.

As discussed above, the claims, by virtue of the recited delivery rates and administration periods, require use of a highly concentrated formulation of fentanyl or fentanyl congener. Such a high concentration formulation would be unnecessary in the context of a device such as Nelson's which operates by diffusion and is designed for local delivery to the neuraxis as opposed to systemic delivery at a site remote from the drug's site of action. Furthermore, because Nelson teaches delivery directly to the drug's site of action, a person of ordinary skill in the art would be directed away from the use of a highly concentrated formulation of a highly potent drug such as fentanyl or a fentanyl congener. Delivery of such a formulation in the immediate vicinity of drug action, e.g., via implantation

in a brain ventricle, would be associated with an extremely high risk of negative side effects. As such, Appellants submit that Nelson teaches away from the claimed invention which, by virtue of the recited delivery rates and administration periods requires use of such a high-concentration formulation.

Claim 84 requires delivery of a composition comprising fentanyl or a fentanyl congener to a subject for 48 hours or more at a low volume rate. Furthermore, Claim 84 indicates that the amount of delivered fentanyl or fentanyl congener is sufficient to establish a systemic analgesic effect in the subject.

There is absolutely no indication in Magruder that the disclosed devices are capable of delivering any composition for 48 hours or more at a low volume rate, much less the compositions of the instant application. In fact, Appellants find no discussion whatsoever in Magruder of any specific volume based delivery rates. Instead, Magruder merely makes the unsupported statement that an object of the invention is to provide a delivery system manufactured as an osmotic device that possesses the ability to deliver the beneficial drug "over a broad range of dosage delivery rates according to the predetermined time-release pattern to the biological recipient over time."[41] Appellants note that Magruder fails to provide even a single example of a volume based delivery rate achieved using its delivery system. The complete lack of disclosure with respect to this required claim element cannot be taken as a suggestion to deliver a composition, much less a fentanyl or fentanyl congener composition, in the manner claimed in the instant application.

As the Examiner relies on Nelson solely for an alleged teaching of the administration of fentanyl and sufentanil, without reference to delivery rates or time periods, the addition of Nelson fails to cure the acknowledged deficiencies in Magruder.

The Examiner asserts, however, that "the amount and delivery rate of the active agent do not impart patentability to the claims, absent evidence to the contrary."[42] The

41 Magruder, column 3, lines 35-42.
42 Final Office Action mailed 3-14-08, page 4.

Examiner also asserts that "[i]t is within the skilled artisan to manipulate the amount of the active agent to achieve a specific delivery profile according to specific patient need."[43]

Claim 84 can be characterized as a method where an exceptionally small volume of a composition containing fentanyl or a fentanyl congener active agent is delivered, yet the method is nonetheless able to achieve therapeutically effective analgesia in the subject. Without reference to the Appellants disclosure, the use of such a low volume rate to achieve analgesia is counter-intuitive, in that one would logically expect that the efficacy of fentanyl/fentanyl congener administration would be negligible at such a low volume delivery rate. Moreover, the Examiner has failed to provide any evidence that a high concentration fentanyl/fentanyl congener formulation sufficient to enable the claimed delivery rates was in the art prior to the March 18, 1999 priority date of the instant application.

Evidence for the above has been provided herein. See, for example, page 4 of the instant application, wherein the Appellants discuss the work of Paix et al. (1995) *Pain* 63:263-9. See also, Paix et al. at page 267, wherein the authors indicate that the delivery of 2200μg of fentanyl in 24 hours required the delivery of a volume of at least 44ml given the available fentanyl formulation. Finally, see the PDR at pages 826 and 831-832, indicating that even after the priority date of the instant application the available fentanyl and sufentanil formulations were of significantly lower concentration than those disclosed in the instant application.

In contrast, the instant application discloses formulations in which fentanyl or fentanyl congener is present at a concentration **substantially higher than conventional formulations**, e.g., current commercially available formulations.[44] See, for example, the instant specification at page 18, line 14 – page 19, line 2; and page 24, line 24 – page 25, line 6, cited previously herein.

Thus, the claimed invention is not simply about manipulating delivery volumes and concentrations of drug. Rather, the claims, by virtue of the recited delivery rates and

43 *Id.*

administration periods, require use of a concentrated formulation of fentanyl or fentanyl congener.

Given the relatively low concentration formulations available prior to Appellants disclosure, a person of ordinary skill in the art would have had no reasonable expectation of success with respect to providing analgesia in a subject via delivery of fentanyl or fentanyl congeners at the low volume rates described in the instant claims.

For the reasons set forth above, Appellants submit that the combination of Magruder and Nelson fails to render Claim 84 *prima facie* obvious. Since Claims 85-91and 94 each depend ultimately from Claim 84, the arguments presented above apply with equal force each of these claims.

As such, the Appellants respectfully request reversal of the rejection of Claims 84-91 and 94 under 35 U.S.C. §103(a).

SUMMARY

Claims 44-99 are not obvious under 35 U.S.C. § 103(a) over Magruder in view of Nelson because the proposed combination fails to teach or suggest each and every element as set forth in the claims, the cited references teach away from the proposed combination and there would have been no apparent reason to combine the references.

---

44 Specification at page 18, lines 14-16.

RELIEF REQUESTED

The Appellants respectfully request that the rejections of Claims 48-99 under 35 U.S.C. § 103(a) be reversed, and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

Respectfully submitted,

Date: April 9, 2008

By: /Michael B. Rubin, Reg. # 61,231/
Michael B. Rubin
Registration No. 61,231

Date: April 9, 2008

By: /Carol L. Francis, Reg. # 36,513/
Carol L. Francis
Registration No. 36,513

F:\DOCUMENT\DURE (Durecl)\007CON2\DURE-007CON2 appeal brief.doc

CLAIMS APPENDIX

48. A method for providing analgesia in a subject, said method comprising delivering a composition comprising fentanyl or a fentanyl congener to the subject, wherein the composition is administered to the subject using an implantable convective delivery system, is delivered from the system for 48 hours or more at a low volume rate of 2 ml/day or less and is sufficient to provide analgesia in the subject.

49. The method of claim 48, wherein the composition is delivered using a patterned delivery regime.

50. The method of claim 49, wherein the composition is delivered in a substantially continuous fashion.

51. The method of claim 49, wherein the composition is delivered in a substantially uninterrupted manner for a pre-selected period of time.

52. The method of claim 49, wherein the composition is delivered in a substantially constant fashion.

53. The method of claim 49, wherein the composition is delivered over an extended period of time.

54. The method of claim 53, wherein the composition is delivered for a period of about 72 hours.

55. The method of claim 53, wherein the composition is delivered for a period from 2 to 5 days.

56. The method of claim 53, wherein the composition is delivered for a period of at least about 100 days.

57. The method of claim 49, wherein the composition is delivered using a controlled drug delivery device.

58. The method of claim of claim 57, wherein the controlled delivery device is implanted in the subject's body.

59. The method of claim 48, wherein the composition is delivered to the subject at a volume rate of from about 0.01 μl/day to about 100 μl/day.

60. The method of claim 48, wherein the composition is delivered to the subject at a volume rate of from about 0.04 μl/day to about 10 μl/day.

61. The method of claim 48, wherein the composition is delivered to the subject at a volume rate of from about 0.2 μl/day to about 5 μl/day.

62. The method of claim 48, wherein the composition is delivered to the subject at a volume rate of from about 0.5 μl/day to about 1 μl/day.

63. A method for providing analgesia in a subject, said method comprising delivering to the subject a composition comprising fentanyl or a fentanyl congener, wherein said fentanyl or fentanyl congener is present in the composition at a concentration of about 0.5 mg/ml to about 500 mg/ml or greater, and further wherein the composition is administered to the subject using an implantable convective delivery system, is delivered from the system at a low volume rate of about 2 ml/day or less and is sufficient to provide analgesia in the subject.

64. The method of claim 63, wherein the fentanyl or fentanyl congener is in solution.

65. The method of claim 64, wherein the fentanyl or fentanyl congener is dissolved in a liquid carrier.

66. The method of claim 63, wherein the composition is administered to the subject as a semi-solid, gel, liquid, suspension, emulsion or an osmotic dosage pharmaceutical formulation.

67. The method of claim 63, wherein the fentanyl or fentanyl congener is present in the composition at a concentration of at least about 2 to at least about 10,000 times greater than the solubility of fentanyl or fentanyl congener in aqueous solution.

68. The method of claim 63, wherein the fentanyl or fentanyl congener is present in the composition at a concentration of from about 0.5 mg/ml to about 500 mg/ml.

69. The method of claim 63, wherein the fentanyl or fentanyl congener is present in the composition at a concentration of from about 1 mg/ml to about 400 mg/ml.

70. The method of claim 63, wherein the fentanyl or fentanyl congener is present in the composition at a concentration of from about 50 mg/ml to about 400 mg/ml.

71. The method of claim 63, wherein the fentanyl or fentanyl congener is present in the composition at a concentration of from about 75 mg/ml to about 300 mg/ml.

72. The method of claim 63, wherein the fentanyl or fentanyl congener is present in the composition at a concentration of from about 100 mg/ml to about 250 mg/ml.

73. The method of claim 63, wherein the composition is delivered at a low volume rate of 2 ml/day or less.

74. The method of claim 63, wherein the composition is delivered using a patterned delivery regime.

75. The method of claim 74, wherein the composition is delivered in a substantially continuous fashion.

76. The method of claim 74, wherein the composition is delivered in a substantially uninterrupted manner for a pre-selected period of time.

77. The method of claim 74, wherein the composition is delivered in a substantially constant fashion.

78. The method of claim 74, wherein the composition is delivered over an extended period of time.

79. The method of claim 78, wherein the composition is delivered for a period from about 2 to about 48 hours.

80. The method of claim 78, wherein the composition is delivered for a period from about 2 to 5 days.

81. The method of claim 78, wherein the composition is delivered for a period of at least about 100 days.

82. The method of claim 74, wherein the composition is delivered using a controlled drug delivery device.

83. The method of claim of claim 82, wherein the controlled delivery device is implanted in the subject's body.

84. A method for providing analgesia in a subject, said method comprising delivering to the subject a composition comprising fentanyl or a fentanyl congener, wherein the composition is administered to the subject using an implantable convective delivery system, the composition is delivered from the system for 48 hours or more at a low volume rate sufficient to deliver from about 0.01 μg/hour to about 200 μg/hour of the fentanyl or fentanyl congener to the subject, and further wherein said amount of delivered fentanyl or fentanyl congener is sufficient to establish a systemic analgesic effect in the subject.

85. The method of claim 84, wherein the fentanyl or fentanyl congener is in solution.

86. The method of claim 85, wherein the fentanyl or fentanyl congener is dissolved in a liquid carrier.

87. The method of claim 84, wherein the composition is administered to the subject as a semi-solid, gel, liquid, suspension, emulsion or an osmotic dosage pharmaceutical formulation.

88. The method of claim 84, wherein the systemic analgesic effect is sufficient to manage pain in the subject.

89. The method of claim 84, wherein the systemic analgesic effect is sufficient to treat pain in the subject.

90. The method of claim 84, wherein the systemic analgesic effect is sufficient to modulate pain response in the subject.

91. The method of claim 84, wherein the systemic analgesic effect is sufficient to ameliorate or alleviate pain in the subject.

92. The method of claim 48, wherein the fentanyl congener is sufentanil.

93. The method of claim 63, wherein the fentanyl congener is sufentanil.

94. The method of claim 84, wherein the fentanyl congener is sufentanil.

95. The method of claim 68, wherein the fentanyl congener is sufentanil.

96. The method of claim 69, wherein the fentanyl congener is sufentanil.

97. The method of claim 70, wherein the fentanyl congener is sufentanil.

98. The method of claim 71, wherein the fentanyl congener is sufentanil.

99. The method of claim 72, wherein the fentanyl congener is sufentanil.

EVIDENCE APPENDIX

The following evidence that qualifies under this heading has been submitted during the prosecution of this application and is attached hereto:

Item 1: Paix et al. (1995) *Pain* 63:263-9, cited in the Information Disclosure Statement filed in the instant application on August 13, 2004, and considered by the Examiner on June 21, 2005.

Item 2: Physician's Desk Reference, Thomson Healthcare, Montvale, NJ, (2001), page 826, cited in the Information Disclosure Statement filed in the instant application on June 20, 2006, and considered by the Examiner on August 24, 2006.

Item 3: Physician's Desk Reference, Thomson Healthcare, Montvale, NJ, (2001), pages 831-832, cited in the Information Disclosure Statement filed in the instant application on June 20, 2006, and considered by the Examiner on August 24, 2006.

Pain, 63 (1995) 263–269

Item 1

PAIN 2874

Clinical Notes

Subcutaneous fentanyl and sufentanil infusion substitution for morphine intolerance in cancer pain management

Andrew Paix [a], Andrew Coleman [b], Judith Lees [c], Jane Grigson [d], Mary Brooksbank [d,e,*], David Thorne [f] and Michael Ashby [d,e]

[a] Chronic Pain Unit, [b] Department of Radiation Oncology, [c] Department of Pharmacy, and [d] Palliative Care Unit, Royal Adelaide Hospital, Adelaide, SA (Australia), [e] Mary Potter Hospice, Calvary Hospital Adelaide, SA (Australia) and [f] Western Palliative Care Service, The Queen Elizabeth Hospital, Woodville, SA (Australia)

(Received 15 December 1994, revision received 12 January 1995, accepted 24 March 1995)

Summary Eleven patients with cancer pain in a palliative care and chronic pain service required cessation of morphine due to unacceptable opioid side effects. In this retrospective study fentanyl was evaluated as a second-line subcutaneously infused opioid. Starting doses ranged from 100 to 1000 μg/24 h, and the duration of fentanyl infusion was 3–70 days. The clinically derived mean relative potency of fentanyl to morphine infusions was 68:1 (SD ± 23; range: 15–100), and we now recommend cautious dose conversion at an approximate equivalence of 150–200 μg fentanyl for 10 mg morphine in non-opioid naive chronic cancer pain patients. All patients demonstrated an improvement in the adverse effect(s) for which the change in opioid was undertaken. Adequate pain relief was achieved in all but 1 patient with mixed nociceptive and neuropathic pelvic pain for whom an epidural infusion of a local anaesthetic/opioid mixture was required. Fentanyl was changed to the more potent synthetic opioid sufentanil in 2 patients for whom the fentanyl dose necessitated too large a volume for the portable syringe driver in use. The clinically derived sufentanil to fentanyl relative potencies were 24:1 and 16:1, respectively. This achieved good analgesia and maintained the favourable side-effect profile seen with fentanyl. Subcutaneous infusion appears to be a safe and viable route of fentanyl delivery, and provided effective analgesia with a low incidence of adverse effects in this small selected group of patients who were intolerant of subcutaneous morphine. We suggest a trial of subcutaneous fentanyl for selected patients who have intractable adverse effects on morphine, and it is now the second-line infusable opioid in our service. Further prospective evaluation of the role of these two synthetic mu opioid agonists in palliative care practice is warranted, as part of an evolving picture of variation in opioid side-effect profile seen with different drugs within the class.

Key words: Cancer pain; Fentanyl; Palliative care; Subcutaneous infusion; Morphine; Adverse effect

Introduction

The World Health Organisation analgesic ladder has established the role of the opioid drug class in cancer pain management and morphine as the drug of first choice in the class (Ventafridda et al. 1987; Walker et al. 1988). The true incidence of opioid side effects experienced by patients receiving morphine for cancer pain is unknown, but all experienced clinicians working in this area will encounter patients for whom nausea and vomiting or impairment of cognitive function are disabling adverse effects which fail to settle in apparent steady state or with a change in the route of drug delivery.

Case histories of patients in whom changes of drug within the opioid class improved the therapeutic ratio by reduction of the side-effect profile have been reported (Galer et al. 1992). They commented on the paucity of clinical research into this phenomenon and the possibility that genetic factors might determine individual opioid responses. Rotation of opioids has shown a similar benefit using rectal methadone (Bruera et al., in press).

* Corresponding author: Dr. Mary Brooksbank, Calvary Hospital, 89 Strangways Terrace, North Adelaide, SA 5006, Australia.

SDI 0304-3959(95)00084-4

Fentanyl is a synthetic phenyl piperidine derivative and a chemical congener of the reversed ester of meperidine. Its pharmacological effects are similar to morphine and meperidine but it is 50–100 times as potent as morphine on a weight basis (Calis et al. 1992). Its shorter duration of action, 30–60 min after a single intravenous dose of 100 μg (AHFS Drug Information 1994), means that continuous infusion is required in chronic pain management. To date fentanyl has only been reported in cancer pain management as a transdermal patch formulation (Herbst and Strause 1992; Zech et al. 1994). There are no reports of documented improvements in side-effect profile when switching from morphine to fentanyl, and no report was found on the use of the more potent synthetic agonist sufentanil for cancer pain.

In this retrospective study, we describe our experience using subcutaneous fentanyl infusions for 11 patients who appeared to have intolerable adverse effects with morphine. Two of these patients were subsequently also changed to sufentanil by subcutaneous infusion and details of this experience are also presented.

Materials and methods

This retrospective survey examined the case notes of 11 patients who had advanced incurable malignancy requiring an opioid drug to control moderate or severe cancer pain. All suffered significant adverse effects necessitating cessation of morphine and its substitution with a continuous subcutaneous infusion (CSCI) of fentanyl. To be eligible for evaluation, all other opioids had to have been discontinued, but the continued use of other non-opioid analgesics at the same or lower dosage was permitted.

Data were collected from the patient case notes and entered into a standardised data collection form. The entries of medical and nursing staff into the case notes were reviewed in order to evaluate the effect of the change to CSCI fentanyl on the incidence and severity of adverse effects and the quality of analgesia. Antiemetic, anxiolytic, and sedative drug requirements were evaluated before and after the change to fentanyl. Efficacy of CSCI fentanyl was assessed by evaluating the degree of pain experienced, the need for non-opioid analgesics and the requirement for breakthrough opioid doses. Visual analogue pain scores (VAS) were also examined in some patients. The nature of the pain was classified as visceral, somatic, neuropathic, or combinations of the above, according to the clinical mechanistic approach to pain classification previously described in this service (Ashby et al. 1992).

Results

The clinical details are summarised in Table I. There were 5 male and 6 female patients, all with advanced malignancies. The mean age was 66.0 years (range: 43–89 years).

Initial opioid treatment was with morphine CSCI (9 patients), morphine by epidural infusion (1 patient) and oral combined paracetamol and codeine (1 patient). All patients required a switch to fentanyl because of significant side effects. These comprised nausea and vomiting (6 patients), delirium (5 patients) and excessive drowsiness and respiratory depression (1 patient).

Starting doses of fentanyl ranged from 100 to 1000 μg/24 h and the duration of use was from 3 to 70 days. Four patients reported better analgesia following the drug change; the other 6 patients reported similar levels of analgesia. One patient with mixed nociceptive and neuropathic pelvic pain was not adequately controlled by morphine or fentanyl CSCI and required an epidural infusion with a local anaesthetic/opioid mixture in the terminal phase. Two patients were changed to sufentanil CSCI when the fentanyl dose requirements necessitated an infusion volume exceeding that which could be administered practically by the portable syringe driver in use (see cases 3 and 4), as the maximum daily infusable dose of undiluted fentanyl is 1100 μg/day per syringe driver. Addition of other drugs to deliver a mixture further reduces fentanyl delivery and compatibilities for subcutaneous infusion with other drugs have yet to be established. The remaining patients remained on fentanyl CSCI until death or separation.

All patients experienced an improvement in the adverse effects which prompted the change to fentanyl. This was assessed by patient reporting, clinical impressions of the attendant medical and nursing staff, and by reviewing the requirements for antiemetics, antipsychotics and other adjuvant medications. Delirium resolved in all 5 affected patients and the incidence and severity of nausea and vomiting was reduced with evidence of fewer reported vomiting episodes and reduced antiemetic requirements. One elderly patient required decreasing fentanyl doses due to persistent drowsiness and the infusion was ceased on the 19th day. There was no serious morbidity attributable to the use of fentanyl in any of the patients studied. No hyperalgesia, myoclonus or rigidity was seen in the study group.

A comparison was made of mean daily doses of morphine and fentanyl required to give stable analgesia (in apparent steady state) before and after the change of drugs. The mean fentanyl/morphine relative potency was 68:1 (SD ± 23; range: 15–100). The relative potency data are shown in Table II.

Four cases are presented in more detail here to illustrate our clinical experience.

Case 1: fentanyl only

A 75-year-old male with adenocarcinoma of the prostate and multiple bony metastases experienced severe bone pain. Adequate relief was obtained with a continuous subcutaneous infusion of morphine, escalat-

TABLE I CLINICAL DATA

TABLE I

CLINICAL DATA

Patient (no.)	Age	Sex	Malignancy	Spread pattern [a]	Nature of pain	Principal opioid analgesic	Route [b]	Dose (mg/24 h)	Reason for change	Other drugs	Fentanyl dose range (μg/24 h)	Days on fentanyl infusion	Analgesia	Resolution of adverse effects [c]	Other comments
1	64	F	adenocarcinoma colorectal	DM: lung LR: abdominal wall	visceral	morphine	CSCI	120	nausea and vomiting inadequate analgesia	Ketorolac Haloperidol Prochlorperazine Aspirin	500–1700	29	better	PR	continued until transfer to nursing home.
2	75	M	adenocarcinoma prostate	DM: bone	somatic	morphine	CSCI	20–30	nausea and vomiting drowsiness	Diclofenac Prochlorperazine Haloperidol Metoclopramide Ketorolac	300–1300	33	better	CR	continued until transfer to nursing home.
3	89	M	non small cell lung	DM: bone liver	somatic and visceral	morphine	CSCI	5–15	delirium	Ketorolac Aspirin	1000	3	unchanged	CR	continued until death.
4	53	F	squamous cell carcinoma cervix	LR: pelvis	visceral and neurogenic	morphine	CSCI	20	delirium, nausea and vomitting	Paracetamol Prochlorperazine	300–4800	68	better	CR: delirium PR: nausea and vomiting	substituted with epidural preterminally due to poor pain control.
5	66	M	non small cell lung	DM: brain bone	somatic	morphine	CSCI	90	hallucinations	Metoclopramide	900	2	unchanged	CR	continued until death.
6	75	F	non small cell lung	LR: chest wall	somatic and neurogenic	morphine	CSCI	15	vomiting	Metoclopramide	25–100	19	unchanged	PR	ceased due to drowsiness.
7	43	F	adenocarcinoma breast	DM: bone	somatic	morphine	CSCI	20–30	vomiting	Haloperidol Prochlorperazine	100–300	37	unchanged	CR	continued until death.
8	71	F	adenocarcinoma endometrium	DM: bone	somatic and visceral	morphine	CSCI	60	drowsiness respiratory depression	Indomethacin	400–700	5	unchanged	CR: respiratory depression PR: drowsiness	continued until transfer.
9	59	F	adenocarcinoma breast	DM: liver	visceral and neurogenic	Paracetamol 500 mg Codeine 30 mg	O	8–12 tablets	delirium inadequate analgesia	Tenoxicam	300–500	20	better	CR: delirium PR: drowsiness	continued until death.
10	69	M	adenocarcinoma prostate	DM: bone	somatic and neurogenic	morphine	CSCI	120	delirium	Haloperidol Metoclopramide	600–2400	70	unchanged	CR	changed to sufentanil CSCI.
11	59	M	adenocarcinoma rectum	LR: bladder psoas	somatic, visceral and neurogenic	morphine	EPI	10	vomiting	Piroxicam Metoclopramide Paracetamol Dexamethasone Haloperidol	800–2400	67	better	CR	changed to sufentanil CSCI

[a] LR = local recurrence; DM = distant metastases.

[b] O = oral; CSCI = continuous subcutaneous infusion; EPI = epidural infusion.

[c] After switch from morphine to fentanyl: CR = complete resolution of effects(s); PR = partial resolution.

TABLE II

CLINICALLY DERIVED RELATIVE POTENCY OF FENTANYL TO MORPHINE (8 patients)

Patient	Mean morphine dose (mg/24 h)	Mean fentanyl dose (μg/24 h)	Potency ratio
1	120	1500	80
2	25	500	50
3	15	1000	15
4	20	350	55
5	70	700	100
6	Never achieved a steady state		
7	25	800	80
8	60	700	85
9	N/A paracetamol and codeine → fentanyl		
10	120	1500	80
11	N/A EPI morphine CSCI fentanyl		

ing from 20 to 30 mg/24 h. At this dose he experienced marked drowsiness and nausea and vomiting which was not controlled with subcutaneous haloperidol or rectal prochlorperazine.

Morphine was replaced by a CSCI of fentanyl at an initial dose of 300 μg/24 h, based on a fentanyl/morphine potency ratio of 100:1. Analgesia was inadequate on this dosage and was escalated to 600 μg/24 h over the next 3 days and resulted in good pain control. Further increases were necessary as his disease progressed and, at separation on the 33rd day of the infusion, his requirements were 1300 μg/24 h.

The patient reported complete relief from nausea and vomiting, allowing haloperidol and prochlorperazine to be ceased on the 2nd day of fentanyl use. Drowsiness resolved within 24 h of ceasing morphine.

Case 2: fentanyl only

A 59-year-old woman with adenocarcinoma of the breast and widespread bony metastases was treated with regular oral combined paracetamol and codeine. At a dose of 8–12 tablets/day (i.e., 240–320 mg codeine) analgesia was inadequate and delirium developed. The patient was known to be sensitive to morphine, having previously developed a marked skin rash, so CSCI fentanyl was commenced at 300 μg/24 h. On the 3rd day of the infusion the dose was increased to 500 μg/24 h due to inadequate analgesia. The patient remained on this dosage for 17 days until separation and reported good analgesia throughout. No breakthrough opioids were required. Delirium resolved within 24 h of ceasing paracetamol and codeine. The patient reported a mild degree of drowsiness associated with the fentanyl infusion. There were no other adverse effects reported.

Case 3: fentanyl and sufentanil

This 69-year-old man had multiple bony metastases from poorly differentiated adenocarcinoma of the prostate. Previous treatment included pelvic radiotherapy, bilateral orchidectomy and single fraction lower

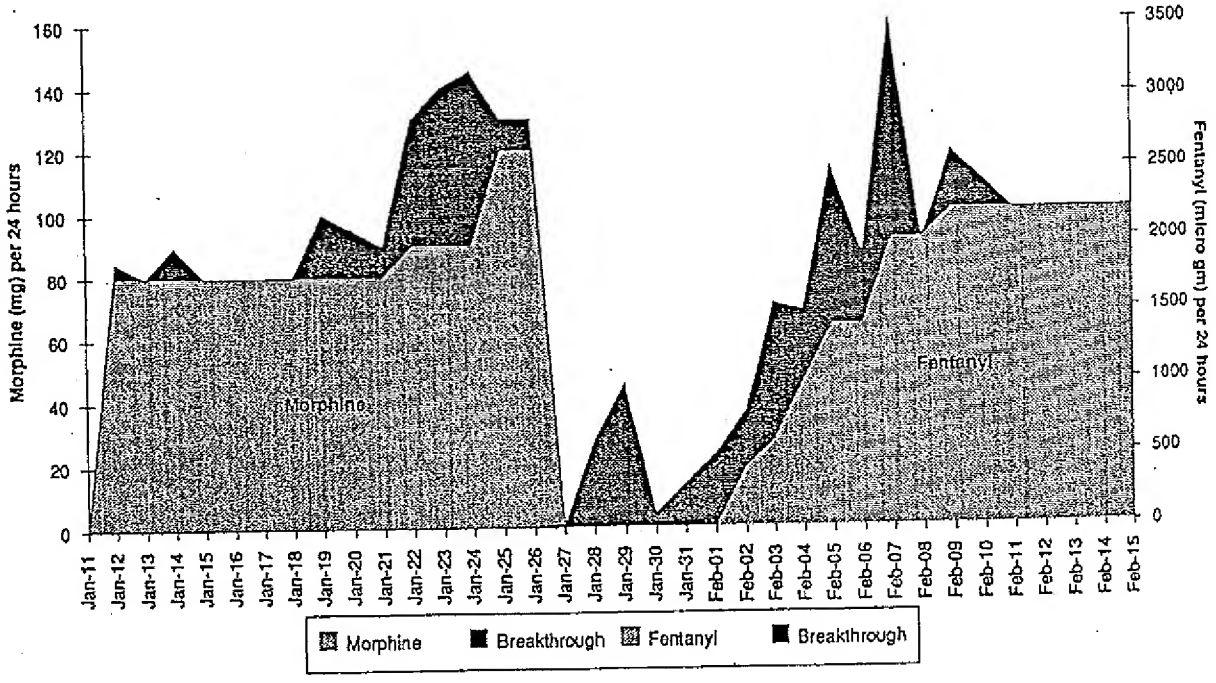


Fig. 1. Plot of morphine and fentanyl use (patient 3, see text).

hemibody irradiation. Pain was becoming incapacitating when he was admitted to hospital and commenced on a multi-agent analgesic regimen that included CSCI morphine at 80 mg/24 h. This provided reasonable analgesia with minimal requests for breakthrough morphine.

After a relatively uneventful week the patient began having short episodes of nocturnal confusion. These become progressively longer until by day 13 they were continuous, culminating in an acute, physically aggressive episode on day 15. Review of his past medical history, physical examination, previous and current drug use and biochemical screen could not identify potential contributing factors other than the morphine infusion. The dose was being titrated to requirements but at the acute episode it was still only 120 mg/24 h.

All medications were ceased, with analgesia being provided by intermittent subcutaneous bolus injections of fentanyl. Within 24 h the delirium had resolved completely while good pain control was maintained. A continuous subcutaneous infusion of fentanyl was commenced and the improved pain control, free from side effects allowed a level of activity and self-care, better than on admission. His increased activity was matched by an increase in the fentanyl requirements to 2200 μg/24 h at the time of discharge. The smallest volume

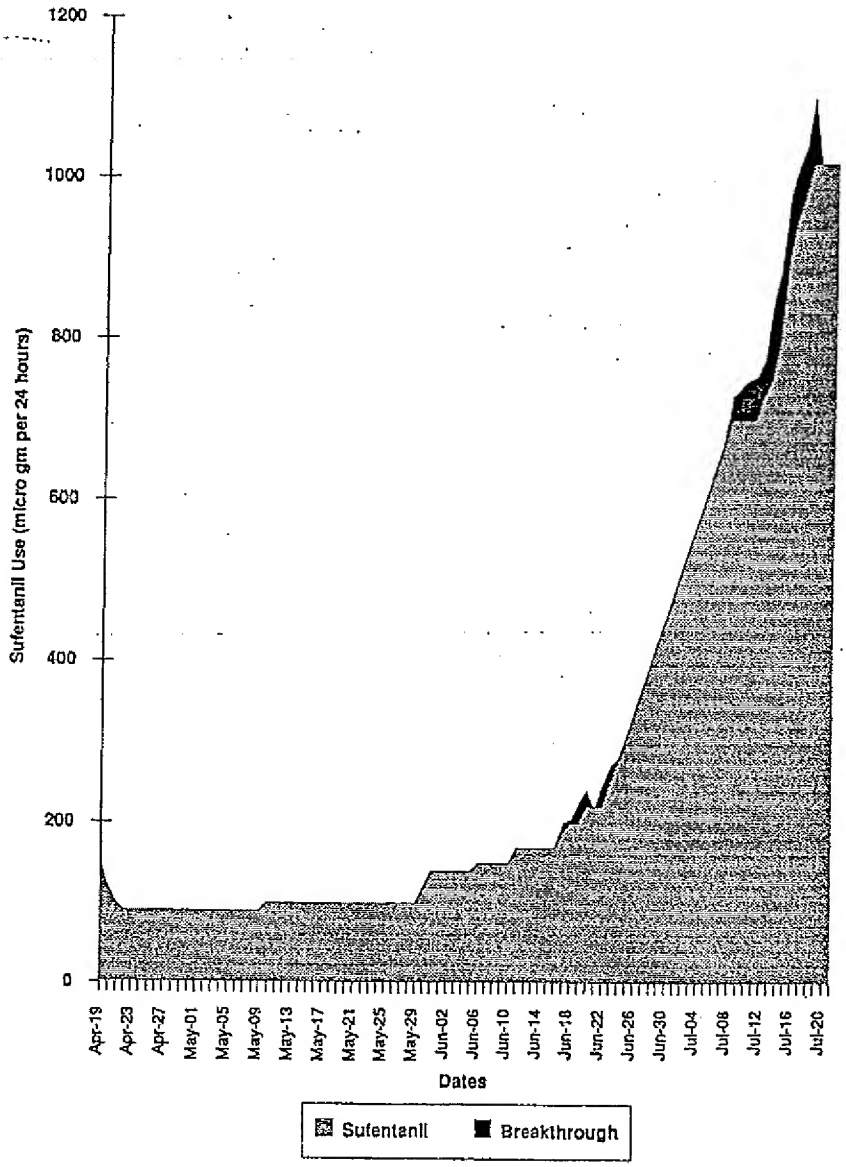


Fig. 2. Plot of sufentanil use (patient 3, see text).

required to deliver this dose was 44 ml, which was divided between two portable syringe drivers driven in parallel and replenished once a day at his home by the Royal District Nursing Service. Preloaded syringes of 100 μg fentanyl for breakthrough pain were provided by the hospital pharmacy. This system worked very well, allowing the patient a wide range of activities including mowing the lawn.

With disease progression, however, the volume of fentanyl required exceeded the capacity of the parallel syringe drivers. The patient was re-admitted to hospital and converted to sufentanil. Equivalent analgesia was achieved at a daily sufentanil dose requiring a single 10-ml syringe driver and suggested a relative potency of sufentanil to fentanyl of 24:1.

Gradual dose increases occurred over the next 50 days until hospital admission was required for terminal care. Sufentanil requirements rapidly increased to over 1000 μg/24 h, without any recurrence of the delirium experienced 5 months earlier on a substantially lower equivalent dose of morphine.

Figs. 1 and 2 show the dose escalation and breakthrough requirements for this patient on morphine, fentanyl and sufentanil sequentially over a period of approximately 6 months.

Case 4: fentanyl and sufentanil

A 59-year-old male with recurrent mucin-producing adenocarcinoma of rectum invading bladder and psoas muscle experienced severe pain from local infiltration and neuropathic pain from L1-L2 involvement. He had been prescribed combined paracetamol and codeine, Methadone, and oral morphine syrup at various times and experienced significant anorexia, nausea, vomiting and sedation in each case. An epidural catheter was inserted and morphine via this route titrated against his pain. Morphine 3 mg epidurally every 12 h was tolerated but failed to provide sufficient analgesia. When increased to 5 mg 12 hourly, the attendant nausea and vomiting was intolerable despite regular anti-emetic therapy, although the previously troublesome sedation was satisfactorily eliminated.

Subcutaneous fentanyl was substituted first by intermittent 2 hourly subcutaneous injection, then via CSCI with added metoclopramide 30 mg/24 h. Initial dose of fentanyl 800 μg/24 h provided adequate analgesia with an absence of nausea, vomiting and sedation. The dose was progressively increased over a period of 67 days to 2400 μg/24 h. At this rate, the volume to be infused via the syringe driver presented technical difficulties and the patient was converted to sufentanil via CSCI. Equivalent analgesia was achieved at 150 μg sufentanil/24 h (relative potency of sufentanil to fentanyl 16:1). Dose requirements for sufentanil increased over the subsequent 97 days to 2000 μg/ 24 h just before his death in his own home. It is of interest that for the latter part of his illness, when sufentanil was utilised, metoclopramide was not required in the syringe driver and nausea and vomiting did not recur.

Discussion

This retrospective study provides evidence that fentanyl is an effective alternative where morphine or combined paracetamol and codeine proved unsatisfactory due to intolerable adverse effects.

Fentanyl was introduced into clinical practice in the 1960s and used in single, small intravenous doses. This method of administration results in a short duration of action and rapid recovery, chiefly due to redistribution into fat stores and a rapid decline in plasma concentrations. This is reflected in its short distribution elimination half-life (T-1/2α) of about 15 min and large volume of distribution (vol. = 4.0 l/kg). Following multiple or large dosing, as the drug approaches steady-state conditions, the terminal half-life (T-1/2β) determines the behaviour of the drug. As T-1/2β is 7–12 h, in the setting of a prolonged CSCI in our patient population, it has an extended duration of action after a change in drug rate or its cessation (Wood and Wood 1990).

The subcutaneous route provides some advantages over the extensively described transdermal route. Two major difficulties have been identified with the transdermal system: a delay of 12–24 h occurs in obtaining steady-state plasma concentrations and a prolonged period of continued fentanyl effect following removal of the patch (Miser et al. 1989). However, there is wide individual variation observed with this route. Portenoy et al. found that steady-state concentrations with repeated patch application every 72 h, were not obtained for 72 h (Portenoy et al. 1993). Other researchers describe problems with difficulty in obtaining adequate pain relief in the first 72 h, inconvenience when attempting to deliver high doses of fentanyl, as the present patch formulation requires an applied surface area of 10 cm^2/25 mg/h of fentanyl delivery (Herbst and Strause 1992) and skin irritation (Zech et al. 1994). Zech concluded that such a delivery system was suitable for to patients with stable pain and low-to-medium opioid dose requirements (Zech et al. 1994).

Fentanyl by continuous subcutaneous infusion may offer advantages in patients with high dose requirements, conditions of the skin that contraindicate the use of patches and those with unstable pain syndromes requiring rapid dose escalation or reduction. Control of pain was achieved rapidly in all the patients studied. The relative potency of fentanyl to morphine from single-dose studies of approximately 100:1 (i.e., 100 μg fentanyl is approximately equivalent to 10 mg morphine in terms of analgesia and side effects generated)

appears to be an overestimate. The mean clinically derived relative potency in this study was 68:1, although the variance was large (SD ± 23) with a wide range of values (15–100). A number of factors make interpretation of this result difficult. It was a retrospective evaluation of a small number of patients, in some of whom the quality of analgesia was better after changing the fentanyl. Additionally, formal testing of pain with VAS was not performed in all patients. Determination of an accurate equianalgesic dose requires stable, good pain control with the drug at steady state. However, we recommend with caution an initial changeover fentanyl dose of 150–200 μg/10 mg of morphine. It should be stressed that this applies only to this highly selected group of patients who are no longer opioid naive and are receiving chronic administration of opioids for cancer pain. It is clear that sufentanil is a substantially more potent drug than fentanyl and we report the first two clinically derived relative potencies (sufentanil and fentanyl) in the literature for chronic cancer pain management of 24 and 16:1 (i.e., 1 μg sufentanil ≈ 1 mg morphine). Clearly these values will need careful review in the light of further experience gained in the clinical use of these drugs for this indication.

There is no doubt that both injectable fentanyl and sufentanil are expensive drugs, and neither is marketed for use in chronic cancer pain at present. In Australia fentanyl costs approximately 5–10 times as much as morphine. At our institution, the hospital acquisition cost of 100 mg morphine is $A0.90, whilst the minimum cost of 1500 μg fentanyl (an approximately equipotent dose in this series) is $A5.20. Costs will vary depending on drug formulation used and individual supply contracts.

We suggest its use for selected patients where subcutaneous or spinal morphine infusion has failed to abolish unacceptable opioid side effects and believe that experience should be reported to government regulation agencies, the manufacturer company (Janssen-Cilag) where appropriate, and in the literature.

Fentanyl and sufentanil via the subcutaneous route are reported as an alternative therapy in a small series of patients who suffered significant side effects associated with the use of morphine. Effective analgesia was associated with a low incidence of adverse effects. Further prospective evaluation of these two opioids in palliative care practice is warranted to clarify their role.

Acknowledgements

The authors thank Megan Ward for typing the manuscript and preparing presentation of data.

Sufentanil was obtained by courtesy of Janssen-Cilag Pharmaceuticals through the Special Access Scheme (Therapeutic Goods Administration, Commonwealth Government, Canberra).

References

AHFS Drug Information, American Society of Hospital Pharmacists, Bethesda, MD, 1994, pp. 1291–4.

Ashby, M.A., Fleming, B.G., Brooksbank, M., Rounsefell, B., Runciman, W.B., Jackson, K. et al., Description of a mechanistic approach to pain management in advanced cancer. Preliminary report, Pain, 51 (1992) 153–161.

Calis, K.A., Kohler, D.R., and Corso, D.M., Transdermally administered fentanyl for pain management, Clin. Pharmacol., 11 (1992) 22–36.

Galer, B.S., Coyle, N., Pasternak, G.W., and Portenoy, R.K., Individual variability in the response to different opioids report of five cases, Pain, 49 (1992) 87–91.

Herbst, L.H. and Strause, L.G., Transdermal fentanyl use in hospice home-care patients with chronic cancer pain. J. Pain Sympt. Manag., 7 (1992) S54–S57.

Miser, A.W. et al., Transdermal fentanyl for pain control in patients with cancer, Pain, 37 (1989) 15–21.

Portenoy, R.K. et al., Transdermal fentanyl for cancer pain, Anesthesiology, 78 (1993) 36–43.

Ventafridda, V., Tamburini, M., Caraceni, A. et al., A validation of the WHO method of cancer pain relief, Cancer, 59 (1987) 850–856.

Walker, V.A., Hoskin, P., Hanks, G.W. and White, I.D., Evaluation of WHO analgesic guidelines in a hospital based palliative care unit, J. Pain Sympt. Manag., 3 (1988) 145–149.

Wood, A.J.J. and Wood, M., Drugs and Anethesia, 2nd edn., 1990, pp. 130–178.

Zech, D.F.J., Lehmann, K.A. and Grond, S., A new treatment option for chronic cancer pain, Eur. J. Palliat. Care, 1 (1994) 26–30.

Item 2

Enlon—Cont.

and 0.2% sodium sulfite as an antioxidant, buffered with sodium citrate and citric acid, and pH adjusted to approximately 5.4.
Enlon® is intended for IV and IM use.

HOW SUPPLIED

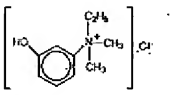
ENLON® (edrophonium chloride injection, USP):
NDC 10019-873-15 15 mL vials
ENLON® (edrophonium chloride injection, USP) should be stored at controlled room temperature 15°–30°C (59°–86°F).

ENLON-PLUS® Ⓡ

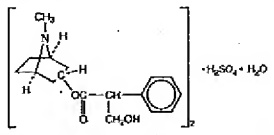
[ĕn '-lon ' plus]
(edrophonium chloride, USP and atropine sulfate, USP)
Injection

DESCRIPTION

Enlon-Plus® (edrophonium chloride, USP and atropine sulfate, USP) Injection, for intravenous use, is a sterile, nonpyrogenic, nondepolarizing neuromuscular relaxant antagonist. Enlon-Plus® is a combination drug containing a rapid acting acetylcholinesterase inhibitor, edrophonium chloride, and an anticholinergic, atropine sulfate. Chemically, edrophonium chloride is ethyl (m-hydroxyphenyl) dimethylammonium chloride; its structural formula is:



Molecular Formula: $C_{10}H_{16}ClNO$
Molecular Weight: 201.70
Chemically, atropine sulfate is:
endo- (±) -alpha- (hydroxymethyl) -8-methyl-8-azabicyclo [3.2.1]oct-3-yl benzeneacetate sulfate (2:1) monohydrate. Its structural formula is:



Molecular Formula: $(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4 \cdot H_2O$
Molecular Weight: 694.84
Enlon-Plus® contains in each mL of sterile solution:
5 mL Ampuls: 10 mg edrophonium chloride and 0.14 mg atropine sulfate compounded with 2.0 mg sodium sulfite as a preservative and buffered with sodium citrate and citric acid. The pH is adjusted in the range of 4.4–4.6.
15 mL Multidose Vials: 10 mg edrophonium chloride and 0.14 mg atropine sulfate compounded with 2.0 mg sodium sulfite and 4.6 mg phenol as a preservative and buffered with sodium citrate and citric acid. The pH is adjusted to the range of 4.4–4.6.

HOW SUPPLIED

Enlon-Plus® (edrophonium chloride, USP and atropine sulfate, USP) Injection should be stored between 15°-26°C (59°–78°F)
NDC 10019-160-05 5 mL ampuls, boxes of 10
NDC 10019-195-15 15 mL multidose vials

ÉTHRANE® Ⓡ

[ĕ 'thrān]
(enflurane, USP)
Liquid For Inhalation

DESCRIPTION

Éthrane® (enflurane, USP), a nonflammable liquid administered by vaporizing, is a general inhalation anesthetic drug. It is 2-chloro-1,1,2-trifluoroethyl difluoromethyl ether (CHF_2OCF_2CHFCl). The boiling point is 56.5° C at 760 mm Hg, and the vapor pressure (in mm Hg) is 175 at 20° C, 218 at 25° C, and 345 at 36° C. Vapor pressures can be calculated using the equation:

$$\log_{10}P_{vp} = A + \frac{B}{T} \qquad A = 7.967 \quad B = -1678.4 \quad T = °C + 273.16 \text{ (Kelvin)}$$

The specific gravity (25°/25° C) is 1.517. The refractive index at 20° C is 1.3026–1.3030. The blood/gas coefficient is 1.91 at 37° C and the oil/gas coefficient is 98.6 at 37° C.
Enflurane is a clear, colorless, stable liquid whose purity exceeds 99.9% (area percent by gas chromatography). No stabilizers are added as these have been found, through controlled laboratory tests, to be unnecessary even in the presence of ultraviolet light. Enflurane is stable to strong base, does not decompose in contact with soda lime (at normal operating temperatures), and does not react with aluminum, tin, brass, iron or copper. The partition coefficients of enflurane at 25° C are 74 in conductive rubber and 120 in polyvinyl chloride.

HOW SUPPLIED

Éthrane® (enflurane, USP) is packaged in 125 and 250 mL amber-colored bottles.
125 mL—NDC 10019-350-50
250 mL—NDC 10019-350-60
Storage: Store at room temperature 15°–30° C (59°–85° F). Enflurane contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years.

ETOPOSIDE Ⓡ

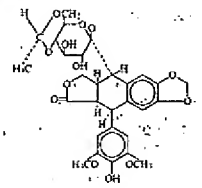
[ē tōpō-side]
Injection

WARNINGS

Etoposide should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Severe myelosuppression with resulting infection or bleeding may occur.

DESCRIPTION

Etoposide (also commonly known as VP-16) is a semisynthetic derivative of podophyllotoxin used in the treatment of certain neoplastic diseases. It is 4'-demethylepipodophyllotoxin 9-[4,6-O-(R)-ethylidene-β-D-glucopyranoside]. It is very soluble in methanol and chloroform, slightly soluble in ethanol, and sparingly soluble in water and ether. It is made more miscible with water by means of organic solvents. It has a molecular weight of 588.56 and a molecular formula of $C_{29}H_{32}O_{13}$.
Etoposide injection is available for intravenous use as 20 mg/mL (100 mg/5 mL and 500 mg/25 mL) in 5 mL and in 25 mL multiple dose vials. The pH of the clear yellow solution is 3.0 to 4.0. Each mL contains 20 mg etoposide, 2 mg citric acid, 30 mg benzyl alcohol, 50 mg polysorbate 80, 650 mg polyethylene glycol 300, and 30.5 percent (v/v) alcohol.
The structural formula is:



HOW SUPPLIED

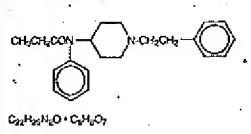
Etoposide Injection is supplied as a sterile, clear, yellow solution, in a 5 mL and 25 mL multi-dose vial.
NDC 10019-930-01, 100 mg (20 mg/mL).
NDC 10019-930-02, 500 mg (20 mg/mL).
Store at controlled room temperature 15°C–30°C (59°F–86°F).

FENTANYL Citrate Injection, USP Ⓒ Ⓡ

[fĕn tăn-ĭl]

DESCRIPTION

Fentanyl Citrate Injection is a sterile, non-pyrogenic solution for intravenous or intramuscular use as a potent narcotic analgesic. Each mL contains fentanyl citrate equivalent to 50 mcg (0.05 mg) fentanyl base in Water for Injection. pH 4.0–7.6; sodium hydroxide and/or hydrochloric acid added, if needed, for pH adjustment. Contains no preservative.
Fentanyl citrate is chemically identified as N-(1-phenethyl-4-piperidyl)propionanilide citrate (1:1) with the following structural formula:



$C_{22}H_{28}N_2O \cdot C_6H_8O_7$ MW 528.60

HOW SUPPLIED

Fentanyl Citrate Injection, USP, equivalent to 50 mcg (0.05 mg) fentanyl base per mL, is available as follows:
2 mL DOSETTE® ampuls packaged in 10s (NDC 10019-038-67)
5 mL DOSETTE® ampuls packaged in 10s (NDC 10019-033-72)
For Intravenous Use by Hospital Personnel Specifically Trained in the Use of Narcotic Analgesics:
10 mL DOSETTE® ampuls packaged in 5s (NDC 10019-034-73)
20 mL DOSETTE® ampuls packaged in 5s (NDC 10019-035-74)
30 mL *SINGLE DOSE* vials packaged individually (NDC 10019-036-52)
50 mL *SINGLE DOSE* vials packaged individually (NDC 10019-037-53)
STORAGE
PROTECT FROM LIGHT
Keep covered in carton until time of use. Store at controlled room temperature 15°–30°C (59°–86°F).
DOSETTE® is a registered trademark of A.H. R... pany.

FLUOROURACIL

Injection, USP
Ⓡ only

WARNING

It is recommended that fluorouracil be given ... under the supervision of a qualified physician ... perienced in cancer chemotherapy and ... versed in the use of potent antimetabolites. ... the possibility of severe toxic reactions, it is ... mended that patients be hospitalized at least ... initial course of therapy.

DESCRIPTION

Fluorouracil Injection, USP, an antineoplastic ... lite, is a sterile, nonpyrogenic injectable solution ... venous administration. Each vial contains 250 ... mg of fluorouracil. Sodium hydroxide and if ... drochloric acid may be added to adjust pH to 9.0–... manufacture.
Chemically, fluorouracil, a fluorinated pyrimi... 5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione. It is a white ... cally white crystalline powder which is sparingly ... water.
The molecular weight of fluorouracil is 130.08.
Molecular formula of fluorouracil is: $C_4H_3FN_2O_2$
The structural formula is:

HOW SUPPLIED

Fluorouracil Injection is available for intravenous ... mL and 5 mL vials. Each 10 mL contains 500 mg ... cil in a colorless to faint yellow aqueous solution. ... contains 250 mg fluorouracil in a colorless to ... aqueous solution. Sodium hydroxide and if necessary ... chloric acid may be added to adjust pH to 9.0–... manufacture.
5 mL single-dose vials, boxes of 10 - NDC 10019-...
10 mL single-dose vials, boxes of 10 - NDC 10019-...

STORAGE

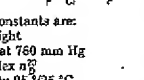
Store at room temperature 15°–30°C (59°–86°F).
PROTECT FROM LIGHT. Retain in carton until ... used. Discard any unused portion.

FORANE®

[for 'ān]
(isoflurane, USP)
Liquid For Inhalation

DESCRIPTION

FORANE® (isoflurane, USP), a nonflammable ... ministered by vaporizing, is a general inhalation ... drug. It is 1-chloro-2,2,2-trifluoroethyl difluorom... and its structural formula is:



Some physical constants are:

Molecular weight	184.5
Boiling point at 760 mm Hg	48.5
Refractive index n_D^{20}	1.3
Specific gravity 25°/25 °C	
Vapor pressure in mm Hg** 20 °C	
25 °C	
30 °C	
35 °C	

**Equation for vapor pressure calculation:

$$\log_{10}P_{mp} = A + \frac{B}{T} \text{ where: } A = 8.056 \quad B = -1684.53 \quad T = °C + 273.15$$

Partition coefficients at 37 °C
Water/gas
Blood/gas
Oil/gas
Partition coefficients at 25 °C—rubber and pla...
Conductive rubber/gas

Item 3

mL fill in 2 mL vial — Packaged in 25s
mL vial* — Packaged in 25s

iection, Chemi-
-a-Hydroxy-α-
echloride, and

ride 10 mg, So-
drate 4.56 mg;
etabisulfite not
r replaced with
ride and/or Hy-

SP: 1¼ (10 mg/

30°C (59°-86°F).
irtion until time
ARD UNUSED

pyrogenic emul-
ble for intraven-
ly described as
ular weight of
clas are:

id; thus, is for-
The pKa is 11.
ctanol is 6761:1
transparent, pro-
an oil (100 mg/
phospholipid (12 mg/
mL) with sodium
table emulsion is

WAYS BE MAIN-
AL INJECTABLE
ERAL PRODUCT
LITE (0.25 MG/
N OF MICROOR-
TAL EXTRINSIC
OL INJECTABLE
GROWTH OF MI-
ITAMICROBIALLY
TANDARDS. AC-
MUST STILL BE
NATION IS SUS-
S AS DIRECTED
E DOSAGE AND
DURES IN FULL
HAVE BEEN RE-
TING TECHNIQUE
ABLE EMULSION
AMINATION OF
ECTION/SEPSIS,
DOR DEATH.

h ready-to-use 20
mL infusion vials

ailable
ackaging
5 vials/shelf tray
0 vials/shelf tray
8 vials/shelf tray
in the presence of
(nitrogen to elim-
ben 4°-22°C (40°-
ed.

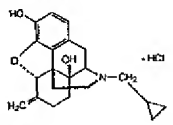
REVEX®

℞

[Re-zĕx]
(nalmefene hydrochloride injection)

DESCRIPTION

REVEX® (nalmefene hydrochloride injection), an opioid antagonist, is a 6-methylene analogue of naltrexone. The chemical structure is shown below:



Molecular Formula: $C_{21}H_{25}NO_3 \cdot HCl$
Molecular Weight: 375.9, CAS # 55096-64-0
Chemical Name: 17-(Cyclopropylmethyl)-4,5α-epoxy-6-methylenemorphinan-3,14-diol, hydrochloride salt.

Nalmefene hydrochloride is a white to off-white crystalline powder which is freely soluble in water up to 150 mg/mL and slightly soluble in chloroform up to 0.13 mg/mL, with a pK_a of 7.6.

REVEX® is available as a sterile solution for intravenous, intramuscular, and subcutaneous administration in two concentrations, containing 100 µg or 1.0 mg of nalmefene free base per mL. The 100 µg/mL concentration contains 110.8 µg of nalmefene hydrochloride and the 1.0 mg/mL concentration contains 1.108 mg of nalmefene hydrochloride per mL. Both concentations contain 9.0 mg of sodium chloride per mL and the pH is adjusted to 3.9 with hydrochloric acid.

Concentrations and dosages of REVEX® are expressed as the free base equivalent of nalmefene.

HOW SUPPLIED

REVEX® (nalmefene hydrochloride injection) is available in the following presentations:
An ampul containing 1 mL of 100 µg/mL nalmefene base (Blue Label) Box of 10 (NDC 10019-315-21)
An ampul containing 2 mL of 1 mg/mL nalmefene base (Green Label) Box of 10 (NDC 10019 311-22)
Store at controlled room temperature.
REVEX® is a registered trademark of Baker Norton Pharmaceuticals, Inc.

ROBINUL® Injectable

℞

(glycopyrrolate injection, USP)

DESCRIPTION

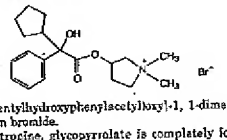
Robinul (glycopyrrolate) is a synthetic anticholinergic agent. Each 1 mL contains:

Glycopyrrolate, USP	0.2 mg
Water for Injection, USP	q.s.
Benzyl Alcohol, NF (preservative)	0.9%

pH adjusted, when necessary, with hydrochloric acid and/or sodium hydroxide.

FOR INTRAMUSCULAR OR INTRAVENOUS ADMINISTRATION.

Glycopyrrolate is a quaternary ammonium compound with the following chemical structure:



3[cyclopentylhydroxyphenylacetyloxyl-1, 1-dimethyl pyrrolidinium bromide.

Unlike atropine, glycopyrrolate is completely ionized at physiological pH values.

Robinul Injectable is a clear, colorless, sterile liquid; pH 2.0–3.0.

HOW SUPPLIED

Robinul® (glycopyrrolate) Injectable, 0.2 mg/mL, is available in
1 mL single dose vials packaged in 25s (NDC 10019-016-81)
2 mL single dose vials packaged in 25s (NDC 10019-016-17)
5 mL multiple dose vials packaged in 25s (NDC 10019-016-54)
20 mL multiple dose vials packaged in 6s (NDC 10019-016-63).

Store at controlled room temperature, between 20°C and 25°C (68°F and 77°F).

Robinul® is a registered trademark of A.H. Robins Company.

SODIUM NITROPRUSSIDE

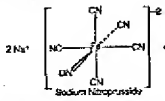
℞

[sōdium nitrō 'prusside]
Injection

Sodium Nitroprusside Injection is not suitable for direct injection. The solution must be further diluted in 5% Dextrose Injection before infusion.
Sodium Nitroprusside Injection can cause precipitous decreases in blood pressure (see DOSAGE AND ADMINISTRATION in full prescribing information). In patients not properly monitored, these decreases can lead to irreversible ischemic injuries or death. Sodium nitroprusside should be used only when available equipment and personal allow blood pressure to be continuously monitored.
Except when used briefly or at low (< 2 µg/kg/min) infusion rates, sodium nitroprusside gives rise to important quantities of cyanide ion, which can reach toxic, potentially lethal levels (see WARNINGS in full prescribing information). The usual dose rate is 0.5–10 µg/kg/min, but infusion at the maximum dose rate should never last more than 10 minutes. If blood pressure has not been adequately controlled after 10 minutes of infusion at the maximum rate, administration of sodium nitroprusside should be terminated immediately.
Although acid-base balance and venous oxygen concentration should be monitored and may indicate cyanide toxicity, these laboratory tests provide imperfect guidance.
The full prescribing information should be thoroughly reviewed before administration of Sodium Nitroprusside Injection.

DESCRIPTION

Sodium nitroprusside is disodium pentacyanonitrosylferrate (2-)dihydrate, an inorganic hypotensive agent whose structural formula is



whose molecular formula is $Na_2[Fe(CN)_5NO] \cdot 2H_2O$, and whose molecular weight is 297.95. Dry sodium nitroprusside is a reddish-brown powder, soluble in water. In an aqueous solution infused intravenously, sodium nitroprusside is a rapid-acting vasodilator, active on both arteries and veins.

Sodium nitroprusside solution is rapidly degraded by trace contaminants, often with resulting color changes. (See DOSAGE AND ADMINISTRATION section of full prescribing information.) The solution is also sensitive to certain wavelengths of light, and it must be protected from light in clinical use.

Each 2 mL of Sodium Nitroprusside Injection contains the equivalent of 50 mg Sodium Nitroprusside Dihydrate in Sterile Water for Injection.

HOW SUPPLIED

Sodium Nitroprusside Injection is supplied as follows in amber-colored, single-dose 50 mg/2mL containers:

NDC 10019-082-02	25 mg/mL vials packaged individually

PROTECT FROM LIGHT. Store in carton until time of use. Light-protective covering enclosed. Avoid excessive heat. Protect from freezing.
Store at controlled room temperature 15°–30°C (59°–86°F).

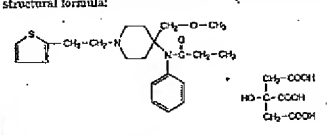
SUFENTANIL CITRATE Injection, USP

℗ ℞

[sū'fĕn-tănil]

DESCRIPTION

Sufentanil Citrate Injection, USP is a sterile, nonpyrogenic, aqueous solution for intravenous and epidural injection. Each mL contains sufentanil citrate equivalent to 50 mcg (0.05 mg) of sufentanil in Water for Injection. pH 3.5–5.0; citric acid added, if needed, for pH adjustment. Contains no preservative. Sufentanil Citrate is a potent opioid analgesic chemically designated as N-[4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide 2-hydroxy-1,2,3-propanetricarboxylate (1:1) with the following structural formula:



$C_{22}H_{30}N_2O_2S \cdot C_6H_8O_7$ MW 578.68

HOW SUPPLIED

Sufentanil Citrate Injection, USP, equivalent to 50 mcg (0.05 mg) sufentanil per mL, is available in the following:

Continued on next page

Sufentanil Citrate—Cont.

1 mL (50 mcg) DOSETTE® ampuls packaged in 10s (NDC 10019-050-43)
2 mL (100 mcg) DOSETTE® ampuls packaged in 10s (NDC 10019-050-21)
5 mL (250 mcg) DOSETTE® ampuls packaged in 10s (NDC 10019-050-05)

STORAGE

PROTECT FROM LIGHT: Keep covered in carton until time of use.

Store at controlled room temperature 15°–30°C (59°–86°F).

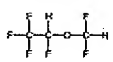
DOSETTE® is a registered trademark of A.H. Robins Company.

SUPRANE®

[s(ə) 'prān]
(desflurane, USP)
Volatile Liquid for Inhalation

DESCRIPTION

SUPRANE® (desflurane, USP), a nonflammable liquid administered via vaporizer, is a general inhalation anesthetic. It is (±)1,2,2,2-tetrafluoroethyl difluoromethyl ether:



Some physical constants are:

Molecular weight	168.04
Specific gravity (at 20°C/4°C)	1.455
Vapor pressure in mm Hg	669 mm Hg @ 20°C 731 mm Hg @ 22°C 757 mm Hg @ 22.8°C (boiling point, typical) 764 mm Hg @ 23°C 793 mm Hg @ 24°C 869 mm Hg @ 25°C

Partition coefficients at 37°C:

Blood/Gas	0.424
Olive Oil/Gas	18.7
Brain/Gas	0.54

Mean Component/Gas Partition Coefficients:

Polypropylene (Y piece)	6.7
Polyethylene (circuit tube)	16.2
Latex rubber (bag)	19.3
Latex rubber (bellows)	10.4
Polyvinylchloride (endotracheal tube)	84.7

Desflurane is nonflammable as defined by the requirements of International Electrotechnical Commission 601-2-13.
Desflurane is a colorless, volatile liquid below 22.8°C. Data indicate that desflurane is stable when stored under normal room lighting conditions according to instructions.
Desflurane is chemically stable. The only known degradation reaction is through prolonged direct contact with soda lime producing low levels of fluoroform (CHF_3). The amount of CHF_3 obtained is similar to that produced with MAC-equivalent doses of isoflurane. No discernible degradation occurs in the presence of strong acids.
Desflurane does not corrode stainless steel, brass, aluminum, anodized aluminum, nickel plated brass, copper, or beryllium.

CLINICAL PHARMACOLOGY

SUPRANE® (desflurane, USP) is a volatile liquid inhalation anesthetic minimally biotransformed in the liver in humans. Less than 0.02% of the SUPRANE® absorbed can be recovered as urinary metabolites (compared to 0.2% for isoflurane).
Minimum alveolar concentration (MAC) of desflurane in oxygen for a 25 year-old adult is 7.3%. The MAC of SUPRANE® (desflurane, USP) decreases with increasing age and with addition of depressants such as opioids or benzodiazepines. (See DOSAGE AND ADMINISTRATION for details).

Pharmacokinetics

Due to the volatile nature of desflurane in plasma samples, the washin-washout profile of desflurane was used as a surrogate of plasma pharmacokinetics. Eight healthy male volunteers first breathed 70% N_2O/30% O_2 for 30 minutes and then a mixture of SUPRANE® (desflurane, USP) 2.0%, isoflurane 0.4%, and halothane 0.2% for another 30 minutes. During this time, inspired and end-tidal concentrations (F_I and F_A) were measured. The F_A/F_I (washin) value at 30 minutes for desflurane was 0.91, compared to 1.00 for N_2O, 0.74 for isoflurane, and 0.58 for halothane (See Figure 1). The washin rates for halothane and isoflurane were similar to literature values. The washin was faster for desflurane than for isoflurane and halothane at all time points. The F_A/F_{A0} (washout) value at 5 minutes was 0.12 for desflurane, 0.22 for isoflurane, and 0.25 for halothane (See Figure 2). The washout for SUPRANE® was more rapid than that for isoflurane and halothane at all elimination time points. By 5 days, the F_A/F_{A0} for desflurane is 1/20th of that for halothane or isoflurane.

Figure 1.
Desflurane Washin

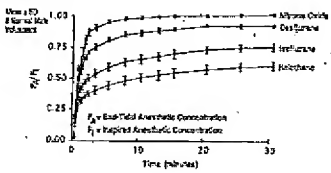
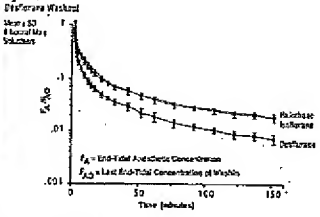


Figure 2.
Desflurane Washout



Pharmacodynamics

Changes in the clinical effects of SUPRANE® (desflurane, USP) rapidly follow changes in the inspired concentration. The duration of anesthesia and selected recovery measures for SUPRANE® are given in the following tables:
In 178 female outpatients undergoing laparoscopy, premedicated with fentanyl (1.5–2.0 µg/kg), anesthesia was initiated with propofol 2.5 mg/kg, desflurane/N_2O 60% in O_2 or desflurane/O_2 alone. Anesthesia was maintained with either propofol 1.5–2.0 mg/kg/hr, desflurane 2.6–8.4% in N_2O 60% in O_2, or desflurane 3.1–8.9% in O_2.
(See first table above)
In 68 unpremedicated outpatients, anesthesia was initiated with thiopental 3–9 mg/kg or desflurane in O_2. Anesthesia was maintained with isoflurane 0.7–1.4%, desflurane 1.8–7.7% in N_2O 50%, or desflurane in O_2.
(See second table above)
Recovery from anesthesia was assessed at 5 minutes following 0.5 MAC desflurane (0.6%) in N_2O 60% using subjective scales. At 30 minutes after anesthesia, only the desflurane group were able to perform the psychomotor tests (p < 0.05) to 76% in the desflurane group (p < 0.05).
(See first table at top of next page)
SUPRANE® (desflurane, USP) was studied in volunteers receiving no other drugs. Hemodynamics were controlled ventilation ($PaCO_2$ 35mm Hg).
(See second table at top of next page)
When the same volunteers breathed spontaneously desflurane anesthesia, systemic vascular resistance, mean arterial blood pressure decreased, while heart rate, stroke volume, and cardiac index (CVP) increased compared to values when they were conscious. Cardiac index, stroke volume were greater during spontaneous ventilation than controlled ventilation.
During spontaneous ventilation in volunteers increasing the concentration of SUPRANE® (desflurane, USP) from 3% to 12% decreased tidal volume and increased arterial carbon dioxide tension and respiratory rate. The combination of N_2O 60% with a given concentration of desflurane gave results similar to those of the same concentration of desflurane alone. Respiratory depression produced by SUPRANE® (desflurane, USP) was similar to that produced by other potent inhalation anesthetics. The use of desflurane concentrations greater than 1 MAC may produce apnea.

EMERGENCE AND RECOVERY AFTER OUTPATIENT LAPAROSCOPY
178 FEMALES, AGES 20-47
TIMES IN MINUTES: MEAN ± SD (RANGE)

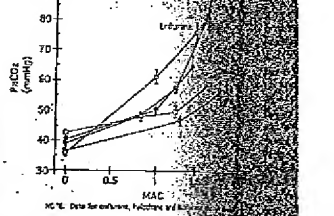
Induction: Maintenance: Number of Pts:	Propofol Propofol/N_2O N = 43	Propofol Desflurane/N_2O N = 44	Desflurane/N_2O Desflurane/N_2O N = 43
Median age	30 (20–43)	26 (21–47)	29 (21–42)
Anesthetic Time	49 ± 53 (8–336)	45 ± 35 (11–178)	44 ± 29 (14–149)
Time to open eyes	7 ± 3 (2–19)	5 ± 2* (2–10)	5 ± 2* (2–12)
Time to state name	9 ± 4 (4–22)	8 ± 3 (3–18)	7 ± 3* (3–16)
Time to stand	80 ± 34 (40–200)	68 ± 55 (30–320)	81 ± 33 (35–190)
Time to walk	110 ± 6 (47–285)	122 ± 55 (37–376)	103 ± 50 (43–220)
Time to fit for discharge	152 ± 75 (66–375)	157 ± 80 (73–355)	150 ± 68 (63–310)

*Differences were statistically significant ($p < 0.05$) by Dunnett's procedure comparing all treatments to propofol/N_2O (induction and maintenance) group. Results for comparisons greater than one hour after surgery differences between groups and considerable variability within groups.

EMERGENCE AND RECOVERY TIMES IN OUTPATIENT SURGERY
46 MALES, 42 FEMALES, AGES 19-70
TIMES IN MINUTES: MEAN ± SD (RANGE)

Induction: Maintenance: Number of Pts:	Thiopental Isoflurane/N_2O N = 23	Thiopental Desflurane/N_2O N = 21	Thiopental Desflurane/O_2 N = 23
Median age	43 (20–70)	40 (22–67)	43 (19–70)
Anesthetic Time	49 ± 23 (11–94)	50 ± 19 (16–80)	50 ± 27 (16–112)
Time to open eyes	13 ± 7 (5–33)	9 ± 3* (4–16)	12 ± 8 (4–33)
Time to state name	17 ± 10 (6–44)	11 ± 4* (6–19)	16 ± 10 (6–46)
Time to walk	195 ± 67 (124–355)	176 ± 60 (101–315)	165 ± 34 (119–259)
Time to fit for discharge	205 ± 53 (153–355)	202 ± 41 (144–315)	197 ± 35 (155–260)

*Differences were statistically significant ($p < 0.05$) by Dunnett's procedure comparing all treatments to isoflurane/N_2O (induction and maintenance) group. Results for comparisons greater than one hour after surgery differences between groups and considerable variability within groups.



RELATED PROCEEDINGS APPENDIX

As stated in the *Related Appeals and Interferences* section above, there are no other appeals or interferences known to Appellants, the undersigned Appellants' representative, or the assignee to whom the inventors assigned their rights in the instant case, which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal. As such this section is left blank.